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ORIGINAL ARTICLE

In silico Evaluation of Anti-Inflammatory Potential of Pyrimidine based Molecules

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ABSTRACT

In silico screening is the process of computer-simulated molecular design screening that aids in identifying structures most likely to bind to medication targets. Utilizing molecular docking techniques, it is possible to examine the interaction of design molecules at a target protein's binding site. After reading several studies on man-made pyrimidine derivatives that have anti-inflammatory properties, the pyrimidine nucleus was created to help the In silico anti-inflammatory study. Several pyrimidine compounds are docked with selected proteins FAAH (4DO3) using computational software in the current studies. In silico experiments (CB DOCK-2). Using protox-II software, the drug likeness (Lipinski's rule of 5) and prediction of toxicity are examined. We determine that the designed molecules follow Lipinski's rule of five since the properties of all the molecules are calculated, the characteristics of the designed derivatives are computed, and they are all within the limit. These molecules were also compared to the standard Epirazole, which had a docking score of -6.6, while the designed molecules had docking scores between -8.0 and -9.5 and acceptable pharmacokinetic properties, so it can be concluded that these molecules may have anti-inflammatory properties.

Keywords: *Pyrimidine, inflammation, anti-inflammatory activity, Insilico screening, Lipinski rule, Protox-II, CB DOCK-II.*

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INTRODUCTION

In both synthetic organic chemistry and pharmaceutical chemistry, pyrimidine derivatives constitute a significant and fascinating class of heterocyclic pharmaceuticals. Furthermore, because pyrimidine derivatives contain heterocycles in the RNA and/or DNA scafold, they have drawn more attention [1, 2]. The word "bioactive" refers to heterocyclic compounds with pyrimidine structures that have many biological effects, such as fighting tumors [5, 6], cell growth [3, 4], viruses [4, 6], inflammation [7], bacteria [8, 9], and tuberculosis [10]. Additionally, vitamins including thiamine, ribofavin, barbitone, and folic acid include the pyrimidine ring [10].

Pyrimidines are responsible for the synthesis of deoxyribonucleotides, which are part of the DNA structure. These nucleotide precursors' analogues have demonstrated antitumor action. Antimetabolic pyrimidine antineoplastic medications have well-established and strikingly comparable mechanisms of action [11]. When these chemicals get into cells through an enzyme-based process in the pyrimidine metabolic pathway, they make chemicals that are similar to biological nucleotides. In conclusion, the

metabolites produced by these activities may inhibit one or more of the enzymes involved in DNA synthesis. Apoptosis may be induced, and DNA damage may result from this [12].

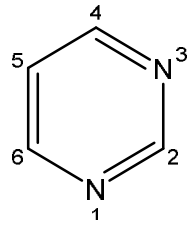


Figure 1: Structure of Pyrimidine

Besides being an important part of DNA and RNA, pyrimidine pharmacophores are also used in a lot of different ways in medicine and science, such as as antibiotics, antibacterials, heart drugs, agrochemicals, and animal products [13]. Researchers found that these derivatives can do many different things, such as stopping irregular heartbeats, blocking serotonin 5-HT6 receptors, reducing inflammation and pain, killing microbes, protecting against the H5N1 influenza virus, the HSV-1 herpes virus, the HAV hepatitis virus, and more (fig. 1). Pyrimidine analogs have previously been shown to be antagonists, anti-conceptive, anti-parkinsonian, and platelet aggregation inhibitors [14].

Pyrimidines' strong biological activity has earned them a distinguished place in chemical and medicinal chemistry. Important biomolecules like DNA and medicines like rosuvastatin, fluorouracil, etravirine, risperidone, iclaprim, and avanafil have pyrimidine cores that make them up [15].

One of the most common types of drugs is nonsteroidal anti-inflammatory drugs (NSAIDs). They work by stopping the enzymes cyclooxygenase-1 (COX-1) and COX-2 from turning membrane-derived arachidonic acid into the prostaglandin endoperoxides PGG2 and PGH2. This reduces pain and inflammation. This process is the first step in making prostanoids, which are lipid messengers that cause inflammation and pain by turning on G protein-coupled receptors on the brain's surface and innate immune cells [16]. The integral membrane enzyme fatty acid amide hydrolase (FAAH) hydrolyzes the fatty acid amide class of lipid transmitters. Some of the substances that FAAH can bind to are oleamide, which is a sedative, anandamide, which is an endogenous cannabinoid, PEA, which is an anti-inflammatory, and OEA, which is a signal that you are full [17]. If FAAH is turned off chemically or by deleting the FAAH gene genetically, higher levels of fatty acid amides are produced. This has a number of behavioral effects, including pain relief, anxiety relief, antidepressant, sleep-improving, and anti-inflammatory phenotypes. The absence of the typical side effects of direct cannabinoid receptor 1 (CB1) agonists, like altered motility, weight gain, or body temperature, is noteworthy. It might be better to stop FAAH from working in order to get the therapeutically beneficial effects of activating the endocannabinoid system without the bad side effects that come with direct CB1 agonists [18, 19]. FAAH is a member of a large enzyme class called the amidase signature class. You can find these enzymes in all living things. They break down amide bonds on a variety of small molecules using a unique Ser-Ser-Lys catalytic triad [20].

Molecules are screened *In silico* using computer simulation to identify those with the highest likelihood of binding to therapeutic targets. It aids in purifying a vast chemical environment. Compared to high-throughput screening, it is more affordable [21]. Molecular docking predicts the intermolecular complex that forms when a drug binds to a receptor or enzyme. This is a good way to figure out what biological activity the drug might have. Using scoring functions, it also determines the binding affinity and forecasts the intensity of the binding as well as the complex's energy [22].

It is the computer modeling of the composition of complexes made up of two or more molecules interacting. Three-dimensional structure prediction is the aim of molecular docking. Molecular docking aims to establish an ideal configuration and relative orientation for the protein and its ligand in order to minimize the overall free energy of the system. Molecular docking is an *In silico* technique that forecasts where tiny molecules or ligands will be located in the target protein's active site (receptor). It has now been widely utilized for virtual screening for the optimization of lead compounds [23, 24]. Primarily, it is employed to precisely estimate the bioaffinities and optimal binding modes of ligands to their respective receptors [25].

A valuable approach that may have a wide range of applications in the drug design process is the docking of diverse chemical entities that are therapeutically significant to the particular target sites. Knowledge of how to visualize binding geometries and interactions is essential for a complete understanding of the structural characteristics that affect how strongly a ligand binds to its receptor [26, 27].

An increasingly crucial tool for drug development is molecular docking. Utilized since the early 1980s, molecular docking has emerged as the prevailing methodology for structure-based drug design. The molecular docking method [27], which simulates the atomic-level interaction between a small molecule

and a protein, can help us understand basic biological processes by letting us know how tiny molecules behave in the binding site of target proteins.

In order for molecular docking to work in real life, you need a way to prepare the ligand as a PDB file and a protein data library with information about the target in the right PDB format. This objective can be achieved through the utilization of diverse software applications (e.g., Discovery Studio), which enable the creation of ligands in PDB format. These instruments categorize ligands based on their affinity for particular target proteins or DNA [28]. Small-molecule molecular docking involves picking out a set number of possible ligand shapes to fit into a certain target groove in order to find the best shape for the complex. Implementing a software scoring function may facilitate this. Spectroscopic methods like nuclear magnetic resonance (NMR), X-ray crystallography, and infrared spectroscopy [29] are used to figure out and look at the three-dimensional structures of biomolecular targets or organic molecules. Therefore, the approximation of the structures of proteins with high sequence homology to known structures is possible via homology modeling. This provides an alternative approach to target structure establishment, which forms the foundation of *In silico* drug discovery [30].

MATERIAL AND METHODS

Ligand selection:

Based on a literature review, we learned that the pyrimidine pharmacophore is quite significant and has a variety of functions; we chose it for its anti-inflammatory properties. We chose this moiety for *In silico* studies since there are numerous synthesized compounds or derivatives of pyrimidine that we are learning about from literature surveys, and further remaining molecules were designed [31].

Protein selection:

Fatty acid amide hydrolase (FAAH) is an enzyme that hydrolyzes the endocannabinoidanandamide [32]. Epirazole inhibits fatty acid amide hydrolase (FAAH), an enzyme that facilitates the intracellular hydrolysis of the endocannabinoidanandamide, in a highly effective and selective manner. Notably, epirazole (Figure 2) selectively stops anandamide oxidation without affecting carrier-mediated uptake. This causes neurons to store more unmetabolizedanandamide, which eventually causes it to leave the cells. Therefore, a significant obstacle for future study is the creation of effective and focused reversible FAAH inhibitors [33, 34].

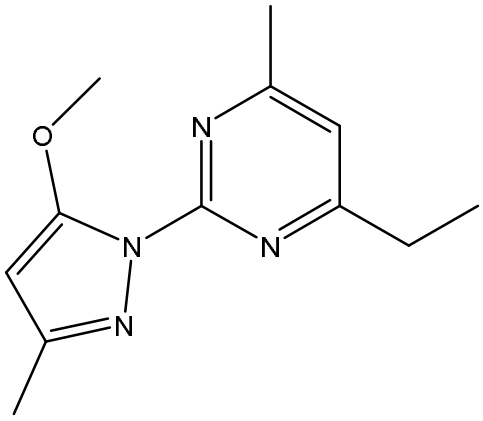


Figure 2: Structure of Epirazole

The structure of FAAH with a non-steroidal anti-inflammatory drug (**4DO3)** was selected for the Insilco study.

Molecular Docking:

The CB DOCK-II software was used to perform the molecular docking experiments involving the chosen ligands. Protein Preparation Wizard was utilized to establish the chosen receptors. The FAAH enzyme and receptor proteins (4DO3) crystal structures were obtained from the Protein Data Bank. During preprocessing, the protein structure was charged up and water molecules were taken out, except for those in the active site. ChemDraw software served as a representation of molecular structures. With the aid of the Ligand preparation assistant application, the ligands were generated. The YASARA2 force field was implemented with the objective of reducing compound geometries and protein structures. Ligand docking was accomplished through the creation of a receptor matrix [35].

ADME properties:

ADME properties contribute significantly to the transformation of a potent lead molecule into a drug. For the lead molecule to be utilized effectively in humans, its absorption, distribution, metabolism, and

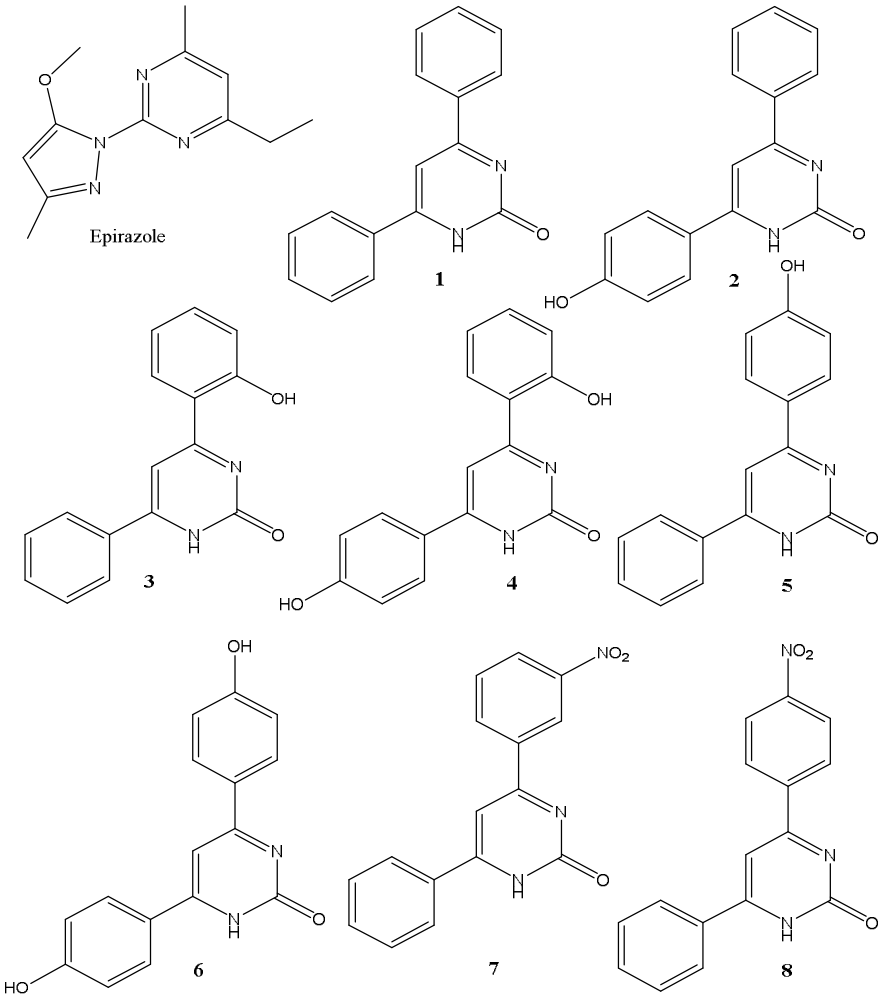
excretion parameters must be fully comprehended. Thus, the ADME properties of specific molecules were predicted using the freely accessible online application Protox-II. Properties like mass, log P, hydrogen bond donar, and hydrogen bond acceptor (Lipinski's Rule of Five) were predicted [36].

Toxicity studies:

The Protox-II server has been used for predicting the ligands' toxicological end points and organ toxicity, as well as their LD50. Utilizing the compound names, an integrated PubChem search (https://pubchem.ncbi.nlm.nih.gov/) was conducted to identify chemical structures. The web server computed the acute toxicity and toxicity targets after selecting the appropriate models. The toxicity prediction was predicated on six distinct targets associated with adverse drug reactions. The compounds' carcinogenicity, hepatotoxicity, immunotoxicity, mutagenicity, and cytotoxicity were assessed [37].

RESULT AND DISCUSSION

The docking simulations showed how different parameters in the protein-ligand interaction profile are important. These parameters include lipophilic and hydrogen bonds, metal interactions, pi-pi interactions, and pi-cation interactions. Scoring functions are quick, approximative math methods used in computational chemistry and molecular modeling to guess how strong the non-covalent interactions will be between two molecules after they have docked. According to force fields based on molecular mechanics and physics, the docking score is the energy of the pose within the binding site. veral things are looked at, such as the solvent effect, changes in the shapes of proteins and ligands, the free energy that comes from the interaction between proteins and ligands, internal rotations, the association energy of ligands and receptors when they form a single complex, and the free energy that comes from changes in the vibrational mode. The specified molecules with protein docking scores have been identified (Figure 3 and Table 1).



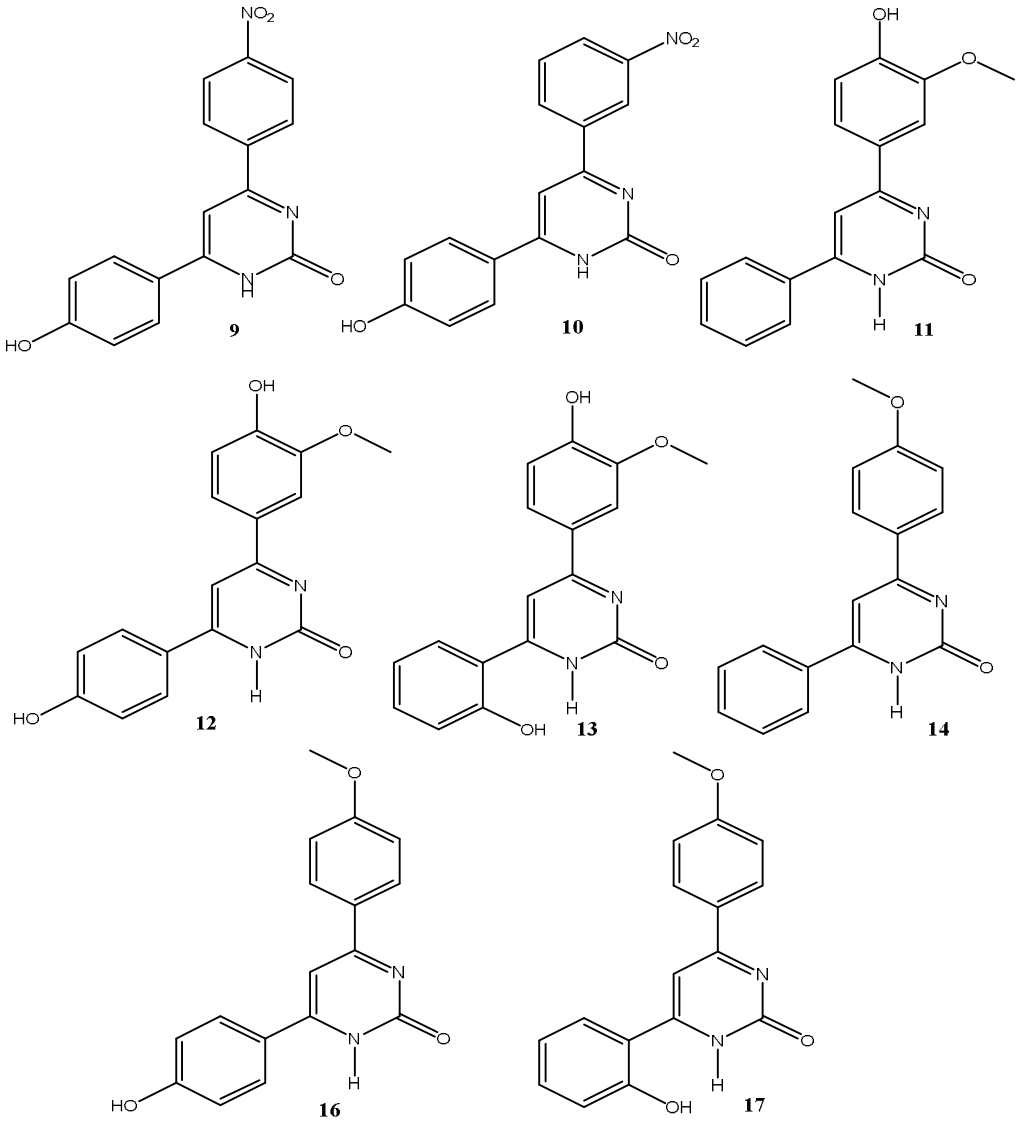


Figure 3: Design molecules for in silico study

Table 1: ADME Properties and Affinity (Docking Score) of pyrimidine molecules

Molecule Number	Compound Number with IUPAC Name	Mass	Log P	H Bond Donor (HBD)	H Bond Acceptor (HBA)	Affinity
Standard						
1.	4-ethyl-2-(5-methoxy-3-methyl-1H-pyrazol-1-yl)-6-methylpyrimidine	234.25	1.3	0	19	-6.6
Pyrimidine Derivatives						
1.	4,6-diphenylpyrimidin-2(1H)-one	248.28	3.1	1	14	-9.2
2.	6-(4-hydroxyphenyl)-4-phenylpyrimidin-2(1H)-one	264.24	2.81	2	15	-8.8
3.	4-(2-hydroxyphenyl)-6-phenylpyrimidin-2(1H)-one	264.28	2.81	2	15	-8.7
4.	4-(2-hydroxyphenyl)-6-(4-hydroxyphenyl)pyrimidin-2(1H)-one	280.28	2.52	3	16	-8.9
5.	4-(4-hydroxyphenyl)-6-phenylpyrimidin-2(1H)-one	264.32	2.94	2	19	-9.1
6.	4,6-bis(4-hydroxyphenyl)pyrimidin-2(1H)-one	280.28	2.52	3	16	-9.2
7.	4-(3-nitrophenyl)-6-phenylpyrimidin-2(1H)-	293.28	3.54	1	15	-9.5

	one					
8.	4-(4-nitrophenyl)-6-phenylpyrimidin-2(1H)-one	293.28	3.54	1	15	-9.2
9.	6-(4-hydroxyphenyl)-4-(4-nitrophenyl)pyrimidin-2(1H)-one	309.28	3.24	2	16	-9.2
10.	6-(4-hydroxyphenyl)-4-(3-nitrophenyl)pyrimidin-2(1H)-one	309.28	3.24	2	16	-9.4
11.	4-(4-hydroxy-3-methoxyphenyl)-6-phenylpyrimidin-2(1H)-one	294.31	2.82	2	18	-8.0
12.	4-(4-hydroxy-3-methoxyphenyl)-6-(4-hydroxyphenyl)pyrimidin-2(1H)-one	310.3	2.52	3	19	-8.4
13.	4-(4-hydroxy-3-methoxyphenyl)-6-(2-hydroxyphenyl)pyrimidin-2(1H)-one	310.3	2.52	3	19	-8.6
14.	4-(4-methoxyphenyl)-6-phenylpyrimidin-2(1H)-one	278.31	3.11	1	17	-8.6
15.	6-(4-hydroxyphenyl)-4-(4-methoxyphenyl)pyrimidin-2(1H)-one	294.31	2.82	2	18	-8.9
16.	6-(2-hydroxyphenyl)-4-(4-methoxyphenyl)pyrimidin-2(1H)-one	294.31	2.82	2	18	-8.4

Table 2:Toxicity prediction of pyrimidine molecule

Sr. No	Molecule	Hepatotoxicity	Carcinogenicity	Immuno-toxicity	Mutagenicity	Cyto-toxicity
Standard						
1	Epirazole (Standard)	Inactive (0.56)	Active (0.56)	Inactive (0.98)	Inactive (0.60)	Inactive (0.85)
Pyrimidine derivatives						
1	1	Active (0.59)	Inactive (0.56)	Inactive (0.97)	Inactive (0.77)	Inactive (0.86)
2	2	Active (0.62)	Inactive (0.55)	Inactive (0.68)	Inactive (0.75)	Inactive (0.84)
3	3	Active (0.59)	Inactive (0.50)	Inactive (0.89)	Inactive (0.76)	Inactive (0.94)
4	4	Active (0.59)	Active (0.50)	Inactive (0.84)	Inactive (0.78)	Inactive (0.94)
5	5	Inactive (0.54)	Inactive (0.58)	Inactive (0.99)	Inactive (0.56)	Inactive (0.69)
6	6	Active (0.62)	Inactive (0.52)	Inactive (0.60)	Inactive (0.76)	Inactive (0.85)
7	7	Active (0.58)	Active (0.69)	Inactive (0.88)	Active (0.82)	Inactive (0.61)
8	8	Active (0.58)	Active (0.59)	Inactive (0.90)	Active (0.82)	Inactive (0.61)
9	9	Active (0.57)	Active (0.58)	Inactive (0.76)	Active (0.82)	Inactive (0.62)
10	10	Active (0.57)	Active (0.58)	Inactive (0.76)	Active (0.82)	Inactive (0.62)
11	11	Active (0.58)	Inactive (0.5)	Inactive (0.55)	Inactive (0.61)	Inactive (0.92)
12	12	Active (0.56)	Inactive (0.52)	Active (0.58)	Inactive (0.62)	Inactive (0.92)
13	13	Active (0.55)	Active (0.50)	Active (0.87)	Inactive (0.66)	Inactive (0.95)
14	14	Active (0.55)	Active (0.51)	Inactive (0.78)	Inactive (0.61)	Inactive (0.83)
15	15	Active (0.59)	Active (0.50)	Inactive (0.55)	Inactive (0.67)	Inactive (0.83)
16	16	Active (0.55)	Active (0.52)	Active (0.86)	Inactive (0.69)	Inactive (0.95)

The docking score-determined design molecules of pyrimidine derivatives were subjected to a comprehensive discussion (Table 1). This discussion centered on their interaction with a specific protein

on the receptor. The 7th molecule, 4-(3-nitrophenyl)-6-phenylpyrimidin2(1H), had the best docking score (affinity) with the FAAH (4DO3) receptor, which is -9.5. This means that these molecules could be used for more in vitro studies. This molecule is also compared with the standard molecule epirazole, which is taken for comparison purposes; the docking score (affinity) of this molecule is -6.6. Also, the docking scores (Affinity) for the other designed molecules were between -8.0 and -9.5, which was a good range for standard Epirazole. The ligand molecule for the FAAH protein also had docking scores in this range. These all-designed molecules, which have an acceptable docking score, may have anti-inflammatory activity (Figure 4a, 4b, 5a and 5b).

The compounds' excessively complex chemical and biological characteristics make it difficult to find new therapeutic candidates for additional lead optimization. Predicting the pharmacokinetic characteristics of drugs therefore becomes crucial.Table 1 lists the *In silico* study results for the pharmacokinetic characteristics of the chosen compounds with the corresponding receptors. Understanding a molecule's pharmacokinetic characteristics is crucial for improving one's chances of finding a new medicine. These characteristics, together with the appropriate ranges, have been determined. The range for molecular weight is 130–725 kDa, and volume is defined as the approximate number of hydrogen bonds that the solute from water will take (500–2000). There should be less than five and ten hydrogen bond donors and acceptors, respectively. The anticipated log p partition coefficient (range: -2.0 to 6.5)

All the previously described features of the developed molecules fell within the acceptable criterion ranges, indicating appropriate pharmacokinetics. Compounds showed hydrogen bond donar and hydrogen bond acceptor values in the specified range. The molecular weight and the predicted partition coefficient are within an acceptable range.

The molecular weight of epirazole is 234.25, and the molecular weight of designed molecules is in the range of 248.28 to 310.3. The log P value of epirazole is 1.3, and that of designed molecules is 2.52 to 3.54. The hydrogen bond donor and acceptor of Epirazole are 0 and 19, respectively, and those of the designed molecules are also in an acceptable range. According to all these calculated properties, all molecules will obey the Lipinski rules of five, which is one of the most important rules for the design of novel molecules.Because of this, studying pharmacokinetics and pharmacodynamics could be very useful for making new experimental models and changing ligands to make them more like drugs (Table 1).

Six distinct targets connected to unfavorable medication interactions served as the basis for the toxicity prediction. It was established which chemicals were hepatotoxic, carcinogenic, immunotoxic, mutagenic, and cytotoxic. Except for compound 5, all compounds are shown to be hepatotoxic. Compounds 4, 7, 8, 9, 10, 13, 14, 15, and 16 are found to be carcinogenic; compounds 12, 13, and 16 are found to have more immunotoxicity, which is shown in the dark red color (values greater than 7 or 70%); and compounds 7, 8, 9, and 10 are found to have more mutagenicity, which is also shown in the red color. Using the PROTOX-II server, the ligands' acute toxicity was examined (Table 2).

Molecular Interactions of Epirazole and Designed Pyrimidine based molecules with FAAH Protein (4DO3)

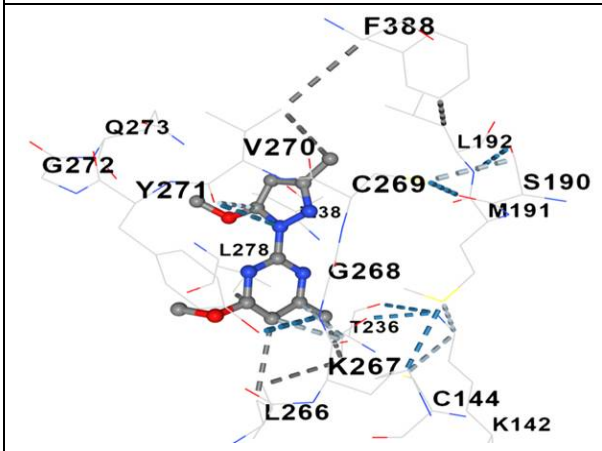


Figure 4a: 3D Representation of drug receptor interaction of Epirazole acid amide hydrolase (4DO3) protein (Backbone Representation).

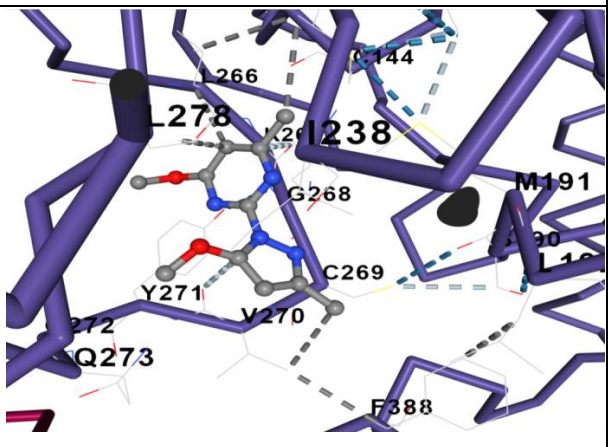


Figure 4b: 3D Representation of drug receptor interaction of Epirazole with fatty acid amide hydrolase (4DO3) protein (Flexible Receptor Representation).

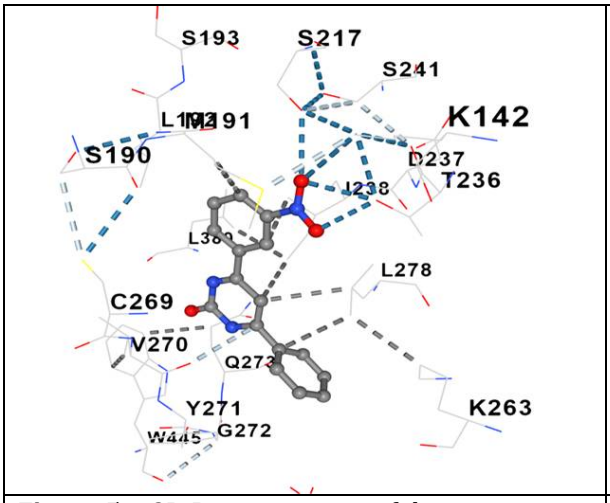


Figure 5a: 3D Representation of drug interaction of 4-(3-nitrophenyl)-6-phenylpyrimidin-2(1H)-one **(7)** with fatty acid amide hydrolase (4DO3) protein(Backbone Representation)..

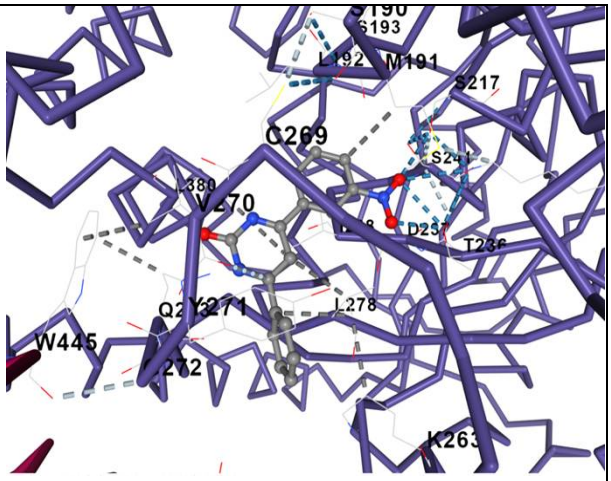


Figure 5b: 3D Representation of drug receptor interaction of 4-(3-nitrophenyl)-6-phenylpyrimidin-2(1H)-one (7) with fatty acid amide hydrolase (4DO3) protein(Flexible Receptor Representation).

CONCLUSION:

It may be concluded that the designed molecules (pyrimidine derivatives) for the *In silico* study against inflammatory enzymes such as FAAH show a good interaction with these receptors and are compared with the standard molecule epirazole. The drug likeness (Lipinski's rule of 5) is checked by using Protox-II software. The properties of designed derivatives are calculated, and the properties of all molecules are within an acceptable range; therefore, it can be concluded that the designed molecules follow Lipinski's rule of 5. If the designed molecules have a good docking score within the range of -8.0 to -9.5 with acceptable pharmacokinetic properties, then these molecules may have anti-inflammatory activity. Using the PROTOX-II server, the ligands' acute toxicity was examined. The results of this study can aid in understanding the molecular mechanism of these compounds as potential leads for anti-inflammatory drugs. Studies conducted in vivo and in vitro can further validate the present findings.

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Not applicable.

Consent for publication:

All the authors approved the manuscript for publication.

Availability of data and material:

All required data is available.

Competing interests:

All authors declare no competing interests.

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