Molecular Docking Study of 3, 4- Dihydropyrimidone Derivatives as Novel Anti-inflammatory Agents

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information
DOI: 10.9734/JPRI/2021/v33i43B32578
Editor(s):
(1) Dr. Paola Angelini, University of Perugia, Italy.
(2) Tanveer Hasan, Shia Post Graduate College, India.
(3) Şahan Saygi, Near East University, Cyprus.
Complete Peer review History: https://www.sdiarticle4.com/review-history/73898

Received 01 July 2021
Accepted 11 September 2021
Published 15 September 2021

ABSTRACT

Aim: Currently, researchers have developed a lot of new active substances as anti-inflammatory agents. One of the target proteins for anti-inflammatory agents is the selective COX-2 active site. Selective COX-2 inhibition is the regulator of the inflammatory reaction cascade. In this research, 3, 4- Dihydropyrimidone derivatives were used to design the anti-inflammatory agent through a selective COX-2 inhibition. The potential activity of 3, 4- Dihydropyrimidone derivatives maybe increase due to the preparation of the Schiff base with aromatic aldehydes. Selective COX-2 inhibition was required to predict their anti-inflammatory activity so, the aim in the present study, molecular docking study of 3,4- dihydropyrimidone derivatives have performed using COX-2 enzyme active site.

Methodology: The molecular docking of 3, 4-dihydropyrimidone derivatives were carried out using AutoDock vina Ver.1.1.2. Twenty 3,4-dihydropyrimidone derivatives were docked into the COX-2 active site with Protein data bank code 3LN1. The interactions were evaluated based on the docking score. Celecoxib was used as the reference standard for this study.

Results: Twenty 3, 4- dihydropyrimidone derivatives showed the approximate docking score -8.4 to -10.1 kcal/mol. Fourteen 3,4-dihydropyrimidone derivatives have a greater docking score compared to celecoxib used as a standard compound. Derivative D-1 had higher binding energy than other 3,4-dihydropyrimidone derivatives because it has the smallest docking score.

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Conclusion: All new 3,4-dihydropyrimidone derivatives are feasible to synthesize and performed their in-vitro evaluation.

Keywords: 3, 4- Dihydropyrimidone; COX-2; Anti-inflammatory; celecoxib; docking.

1. INTRODUCTION

The inflammatory process in the body serves a significant function in the control and repair of injury. Commonly referred to as the inflammatory cascade or simply inflammation. The two types of inflammatory conditions are acute and chronic. Acute inflammation arises as to the initial response to tissue injury, being facilitated by the release of various autacoids like histamine serotonin, leukotrienes, and thromboxanes. Common indications are observed in acute inflammation include swelling, redness, pain, heat, and immovability. Acute inflammation can be caused by diseases and certain conditions including abrasion or cut on the skin, acute bronchitis, achy throat from flu or cold, infected ingrown toenail, acute appendicitis, dermatitis, sinusitis, tonsillitis, infective meningitis, high-intensity exercise, and physical trauma. The chronic inflammatory process involves the release of various mediators such as tumor necrosis factor-α, interferon, interleukins, and cytokine that plays a crucial role in this kind of inflammatory process. Chronic inflammation may lead to the development of certain diseases i.e. cardiovascular diseases, cancer, diabetes, rheumatoid arthritis, allergies, tuberculosis, hepatitis, periodontitis, chronic obstructive pulmonary disease (COPD), asthma, and chronic peptic ulcer [1]. Worldwide, 3 out of 5 individuals die due to chronic inflammatory diseases like diabetes, chronic respiratory diseases, heart disorders, stroke, obesity, and cancer.

Non-steroidal anti-inflammatory (NSAID) and steroidal drugs are commonly used for the treatment of pain and inflammation associated with different diseases like cancer-related pain, arthritis, etc. NSAIDs are used for a larger duration may cause GIT ulceration, bleeding, and renal injury [2]. These adverse effects are observed in marketed drug formulations due to non-selective inhibition of cyclooxygenase isoenzyme. Steroids are significant anti-inflammatory agents but are reported to have severe adverse effects such as liver cancer, weight gain, enlargement of the heart, etc. In case of severe pain, steroidal drugs and NSAIDs are used along with opioid analgesics. The severity of NSAIDs adverse effects is experiencing more in the immune compromised patients suffering from life-threatening illnesses like cancer, HIV/AIDS, etc [3]. Although there are several anti-inflammatory drugs available in the market therefore, there is a need to develop novel drugs with a better safety profile.

The heterocyclic compounds cover a large area of research in the field of medicinal chemistry. They have played a crucial role in developing numerous therapeutic agents in medicinal chemistry. These agents are typically available in nature and are an essential part of daily life in various ways. In the center of them have oxygen-, nitrogen-, and sulfur-containing heterocyclic derivatives work as an exclusive and multipurpose scaffold for experimental drug design. Pyrimidine is the most important heterocycles moiety that exhibits several biological activities [4]. In 1893, Pietro Biginelli was synthesized the 3,4-dihydropyrimidin-2(1H)-one first time through a one-pot three-component cyclo-condensation reaction of 3-hydroxyl benzoaldehyde, ethyl acetoacetate, and urea under the acidic condition in ethanol [5].

The 3, 4- Dihydropyrimidone became important class in the field of medicinal chemistry due to their various pharmacological and biological activities such as antibacterial [6], antifungal [7], antiparasitic [8], antitubercular agents [9], antiviral [10], antimuscarinic [11], anticonvulsant activities [12], antithyroid [13], antimalarial agents [14], calcium channel blockers [15, 16], antihypertensive [17], hypolipidemic [18], antioxidant [19], anti-inflammatory [20], anticancer [21], antiangiogenic [22] as well as inhibits enzymes like urease [23], acetylcholinesterase [24] and acts as an agonist on the GABA receptor [25].

Although the exact mechanisms of action of 3, 4- Dihydropyrimidone derivatives remain unknown, a study in inflammation indicated that 3, 4-dihydropyrimidone can inhibit the action of COX-2. The main objective of the present study was thus to examine the 3, 4- Dihydropyrimidone derivatives and COX-2 interaction and to identify the consequence of COX-2 inhibition in case of inflammation. Docking analysis was also
executed to define the residues involved in 3, 4- Dihydropyrimidone regulatory action on COX-2.

2. EXPERIMENTAL DETAILS

2.1 Preparation of Target Protein X-ray Structure

The crystal structure of the celecoxib bound at the COX-2 active site (PDB ID: 3LN1) was selected as the target protein downloaded from http://www.pdb.org/.

2.2 Design of Novel 3, 4- Dihydropyrimidone Derivatives

The role of the new drug development is (a) determining pharmacophore, (b) changing the substituent of pharmacophore (c) finalised the list of new substituents. In this study, 3, 4- Dihydropyrimidone is a novel pharmacophore and an anti-inflammatory agent. The Substituents are selected for designing new derivatives. A 2-furyl ring is present at the 4th position of 3, 4- Dihydropyrimidone and then Dihydropyrimidone converted into Hydrazide. This hydrazide is used for the preparation of Schiff base using substituted aromatic aldehydes. Aromatic aldehydes are consist of different substitutions such as 4-NO2, 4-NH2, 4-Cl, 4-Br, 3,4,5- trimethoxy, 4-CF3, 4-OCH3, etc.

2.3 Ligands Preparation

The structures of 3, 4- Dihydropyrimidonedervatives D1-D20 (Fig. 1) were drawn by using Chem Draw Ultra 8.0 (Cambridge Soft). The 2D structures of compounds were converted to the 3D structure utilizing Chem 3D Ultra 8.0. The optimization of molecules and minimization geometry of the ligands was performed using DFT method and saved as PDB format, to be read by the AutoDock vina program.

2.4 Molecular Docking Studies

Molecular docking is an important tool in structural molecular biology and computer-aided drug design. The main aim of molecular docking is to predict the predominant binding mode(s) of a ligand with a target protein of a known three-dimensional structure. Effective docking methods search high-dimensional spaces successfully and use a scoring function that correctly ranks molecules that are utilized for the study. Docking can be used to perform virtual screening on huge libraries of molecules, rank the results, and propose structural hypotheses of how the ligands bind to the target protein and exhibit its action, which is helpful in lead optimization. The study of 3, 4- Dihydropyrimidone derivatives and COX-2 active site interaction were evaluated by using molecular docking techniques on AutoDock vina Version 1.1.2. We used the crystal structure of the celecoxib bound at the COX-2 active site (code 3LN1, http://www.pdb.org/) as the target protein. Before screening the ligands, the docking protocol was validated by re-docking the 3LN1 ligand into its binding pocket within the COX-2 crystal to obtain the docked pose and RMSD.

3. RESULTS AND DISCUSSION

Virtual screening is a technique to identify novel bioactive molecules from large chemical libraries through computational means by applying knowledge about the target protein. Molecular docking is used in the current drug design process to understand the interaction between target proteins and ligands. These techniques are supported by the design of a new drug that has specific pharmacological activity by the mechanism of drug-receptor interaction. Computer-aided drug design supports the identification of small molecules by orienting and scoring them in the active site of the target protein. The docking simulation technique was performed by using AutoDock vina Version 1.1.2 with 3, 4- Dihydropyrimidone derivatives, and they were docked with COX-2 as the target protein. This program selected the best docked based on two criteria such as ligand binding position and fitness function scores comparison. The parameter to identify the best ligand binding position was the root-mean-square distance (RMSD).

A docking score is a value that imitates the binding energy required to form a bond between the target protein and ligand, which predicts the activity of compounds and should be stable. The binding energy value of 3, 4- Dihydropyrimidone derivatives are shown in Table 1. Twenty3, 4- Dihydropyrimidone derivatives showed the approximate docking score -8.4 to -10.1 kcal/mol. Fourteen3, 4- Dihydropyrimidone derivatives which values that have a greater docking score compared to celecoxib used as a standard. Derivative D-1 had higher binding energy than other 3, 4- Dihydropyrimidone derivatives.
because it has the smallest docking score (-10.1 kcal/mol).

All 3, 4- Dihydropyrimidone derivatives have hydrogen bond interaction with protein residue. One of them which have the lower docking score is compound D-1. Compound D-1 was substituted with the 4-Nitro group at R. This means it has higher binding energy to interact with the target receptor. The interaction of celecoxib (Fig. 2) and compound D-1 (Fig. 3) with COX-2 active site and their hydrogen bonds are shown below. From these interaction results, it was found that the celecoxib and compound D-1 binds to common amino acid residue found in COX-2 active sites like Ser B129, TRP B125, and Leu B131.

![Fig. 1. General Structure of 3, 4- Dihydropyrimidone derivatives](image)

Table 1. Docking Score of 3, 4- Dihydropyrimidone derivatives with COX-2 active site

| Ligand | Binding Affinity (kcal/mol) | Ligand | Binding Affinity (kcal/mol) |
|--------|----------------------------|--------|----------------------------|
| D-1    | -10.1                      | D-11   | -8.8                       |
| D-2    | -8.5                       | D-12   | -8.6                       |
| D-3    | -9                         | D-13   | -8.8                       |
| D-4    | -9.2                       | D-14   | -9.3                       |
| D-5    | -8.6                       | D-15   | -9                         |
| D-6    | -8.8                       | D-16   | -9.4                       |
| D-7    | -9                         | D-17   | -8.9                       |
| D-8    | -8.4                       | D-18   | -8.4                       |
| D-9    | -9                         | D-19   | -8.9                       |
| D-10   | -8.5                       | D-20   | -9.1                       |
| Std    | -8.6                       |        |                            |

![Fig. 2. 3D &2D structure of celecoxib interact with COX-2 active site](image)
4. CONCLUSION

Twenty molecular structures of 3, 4-Dihydropyrimidone derivatives possessing furan ring at 4th position of pyridine ring and their hydrazide derivative was used to prepared Schiff base using substituted aromatic aldehydes have been docked and score obtained to identify the ligands that bind to COX-2 protein structure. The result shows that fourteen derivatives showed a higher docking score than celecoxib. It means they have higher binding energy interaction with the target protein. Therefore, these compounds could be considered potent anti-inflammatory agents. For further investigation, synthesis and in vitro evaluation are required to get anti-inflammatory activity.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/73898