Research Article

Molecular docking study of Chalcone hydrazide derivatives as novel Anti-inflammatory agent

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ABSTRACT

Researcher have recently discovered a variety of new active compound that show potential as anti-inflammatory drugs. One of the target proteins for anti-inflammatory drugs is the selective COX-2 active site. The inflammatory reaction cascade is regulated by selective inhibition of COX-2. This study employed selective COX-2 inhibition to create an anti-inflammatory drug using derivatives of chalcone hydrazide. In order to predict the anti-inflammatory effect of these compounds, selective COX-2 inhibition was necessary. For this reason, the current study's goal was to molecularly dock these derivatives using the active site of the COX-2 protein. Chalcone hydrazide derivatives were molecularly docked using Auto-Dock vina Ver.1.1.2. Using the Protein Data Bank code 3LN1, thirty Chalcone Hydrazide derivatives were docked into the active site of the cox-2 enzyme to assess their potential binding and inhibitory activity. For this investigation, celecoxib served as the reference standard. The approximate docking score of thirty Chalcone hydrazide derivatives was -8.4 to -10.1` kcal/mol. Comparing 30 Chalcone hydrazide derivatives to celecoxib as a reference chemical, the former has a higher docking score. Because derivative (CH-9) has the lowest docking score, it has a larger binding energy than other derivatives of Chalcone hydrazide. Every novel derivative of Chalcone hydrazide that is synthesized and evaluated in vitro.

Keyword: anti-inflammatory, chalcone hydrazide, celecoxib, cox-2, docking

INTRODUCTION

Inflammation is a biological response to any adverse stimulus, such as tissue damage and infection. The transport of blood components to the illness or injury site causes vasodilation and enhanced vascular permeability [1].

Inflammation is a complex biological response that can be categorized as either acute or chronic. It involves a series of biochemical reactions that impact the local blood vessels, immune system, and various cell types in damaged tissue. Acute inflammation is characterized by elevated levels of plasma proteins in the blood and the migration of innate immune cells, like neutrophils and macrophages, to the affected area. Chronic inflammation, on the other hand, is marked by a shift in the types of cells present at the site of inflammation and involves a simultaneous process of tissue destruction and repair [2].

Inflammation linked to many illnesses, such as arthritis and cancer-related discomfort, are frequently treated with steroidal and non-steroidal anti-inflammatory medications (NSAIDS). Extended use of

NSAIDS may result in bleeding, GIT ulceration, and kidney damage [3]. These side effects are a result of non-selective inhibition of the cyclo-oxygenase isoenzyme in commercially available medication formulations. Although steroids have been shown to have serious side effects, including weight gain, liver cancer, heart enlargement, and other conditions, they are nevertheless important anti-inflammatory drugs. In addition to opioid analgesics, NSAIDS and steroidal medications are utilized when pain is severe. Immunocompromised individuals with life-threatening diseases including cancer, HIV/AIDS, etc. Are particularly susceptible to the severe side effects of NSAIDS [4]. Despite the fact that there are many anti-inflammatory medications on the market, new medications need to be developed with improved safety profiles.

The word "chalcone" comes from the Greek word "chalcos" which meaning "bronze."In the late 1800s, a research lab produced the first chalcones. Chalcones (benzalacetophenone) are made up of two rings enclosing an enone system. Chalcones are found naturally in a wide variety of plants, including fruits, vegetables, spices, and tea. They are particularly abundant in the flavonoid family of plants, where they serve as a precursor for biosynthesis [5].

Clinical studies on chalcones showed decreased clinical signs and symptoms, high bioavailability, and a general lack of side effects. Compounds with these properties have beenshown to have a wide range of biological and pharmacological activities, including antimicrobial [6], anti-ulcerative [7], anti-inflammatory [8], antiviral [9], antitumor [10], antimalarial [11], antibacterial [12], antioxidant [13], antifungal [14], anti-diabetic [15] , anti-hyperlipidemic[16][17] , anti-protozoal [18] , anti-tubercular[19] and Chalcones are still the subject of extensive scientific study.

Experimental Details:

Preparation of Target Protein X-ray Structure:

The X-ray crystal structure of the cox-2 in which the celecoxib bound at the active site (PDB ID: 3LN1) was designated as the target protein taken from https://doi.org/10.2210/pdb3LN1/pdb.

Design of Novel chalcone hydrazide Derivative:

Identifying the pharmacophore, changing the pharmacophore's substituent, and generating a list of novel substituents are the three steps in the innovative drug development process. In this study chalcone hydrazide are pharmacophores as the anti-inflammatory agent. The several substituents designated for designing novel analogues contain -Cl, -CF3, -NO2, -CH3, -CH (CH3)2, -NH2, -OCH3 and so on.

Preparation of Ligands:

Chem Draw Ultra 8.0, developed by Cambridge Soft, played a crucial role in crafting chalcone hydrazide derivatives such as CH-1 to CH-30. Additionally, Chem 3D Ultra 8.0 was employed to translate the initial 2D structure of the proposed ligand into a 3D model. To refine the ligand's structure, the semi-empirical PM3 method was employed to optimize and minimize its energy, ensuring an RMS gradient of 0.001 KCal/mol at the termination, with a maximum of 1000 repetitions. The resulting configuration was saved in PDB format for compatibility with the AutoDock Vina program [24]. Subsequently, the Swiss ADME tool was utilized to assess the drug-likeness of the compounds. These computational steps aimed to enhance our understanding of the molecular structures and properties of pyrazole derivatives, thereby facilitating their development.

Molecular Docking Studies:

Protein ligand docking is an essential tool in computer-aided drug design and structural molecular biology since it can anticipate the most likely ligand binding modalities with target proteins that have known three-dimensional structures. Docking methods employ scoring systems to explore high-dimensional spaces efficiently and accurately score the molecules under study. This is useful for lead optimization because it allows for the visualization of big compound libraries, scoring of outcomes, and the acquisition of structural insights into the ways in which ligands interact with target proteins to produce their effects. In this study, AutoDock Vina Version 1.1.2 was used for molecular docking to investigate the relationship between COX-2 active site contacts and Chalcone hydrazide derivatives. The crystal structure of celecoxib bound at the COX-2 active site (PDB code 3LN1, https://doi.org/10.2210/pdb3LN1/pdb) served as the target protein. The 3LN1 ligand was redocked into the COX-2 binding pocket to validate the docking method before ligand screening.

Results and Discussion

Virtual screening is a computational method that uses target protein information to find new bioactive compounds from massive chemical libraries. The current medication design approach makes use of molecular docking to comprehend how ligands and target proteins interact. The development of a novel medication with targeted pharmacological action through the mechanism of drug-receptor interaction supports these approaches. Small compounds are identified with the use of computer-aided drug design, which scores and aligns them in the target protein's active site. employing Auto-dock vina version 1.1.2., the docking simulation technique was carried out with Chalcone hydrazide derivatives,

employing COX-2 as the target protein. Based on two factors, such as the comparison of fitness function scores and the location of ligand binding, this software chose the best docked. The root-mean-square distance (RMSD) was the criterion used to determine the optimal ligand binding location.

Modern drug design processes employ molecular docking to determine how ligands and receptors interact. These techniques help in the development of novel drugs with targeted activity through them mechanism of drug-receptor interaction. By positioning and scoring tiny compounds in a target protein's active binding region, computer-aided drug design makes it easier to identify them. The binding energy value of chalcone hydrazide derivatives as shown in table 1. The approximate docking score of all chalcone hydrazide derivatives ranged from -8.4 to -10.1 kcal/mol. Thirty chalcone hydrazide derivatives which shows greater docking value as compared to standard drug celecoxib. In comparison to other chalcone hydrazide derivative CH-9 demonstrated greater binding energy(-10.1kcal/mol).

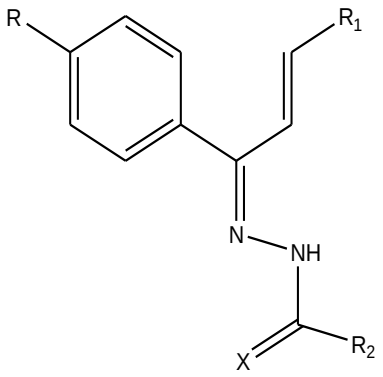

Figure 1: general structure of chalcone hydrazide derivative

Table 1. Docking Score of chalcone hydrazide derivatives with COX-2 active site

DERIVATIVE	**DOCKING SCORE**	**DERIVATIVE**	**DOCKING SCORE**
CH-1	-9.7	CH-16	-9.7
CH-2	9.9	CH-17	-10
CH-3	-9.9	CH-18	-8.9
CH-4	-9.5	CH-19	-9.3
CH-5	-9.3	CH-20	-9.7
CH-6	-10.1	CH-21	-9.7
CH-7	-9.9	CH-22	-9.6

CH-8	-9.7	CH-23	-9.4
CH-9	-10.1	CH-24	-9.7
CH-10	-9.1	CH-25	-9.5
CH-11	-9.8	CH-26	-9.9
CH-12	-9.5	CH-27	-9.9
CH-13	-9.9	CH-28	-9.8
CH-14	-9.9	CH-29	-9.2
CH-15	-9.6	CELECOXIB	-8.4
CH-30	-9.3		

Through hydrogen bonding, all chalcone hydrazide derivatives interact with the residues of proteins. Among those with the lowest docking score is compound CH-9. In the derivative CH-9, the 4-amino acetophenone and 4-methyl benzaldehyde groups, respectively, were used in place of R AND R1. This suggests that it has a greater binding energy when interacting with the target receptor. The following diagram shows the interactions between the hydrogen bonds and the COX-2 active site between derivative CH-9 (Figure 2) and celecoxib (Figure 3). The interaction experiments revealed that both medication CH-9 and celecoxib bind to common amino acid residues located in the active sites of COX-2, which include PRO B528, ARG B29, and GLN A529

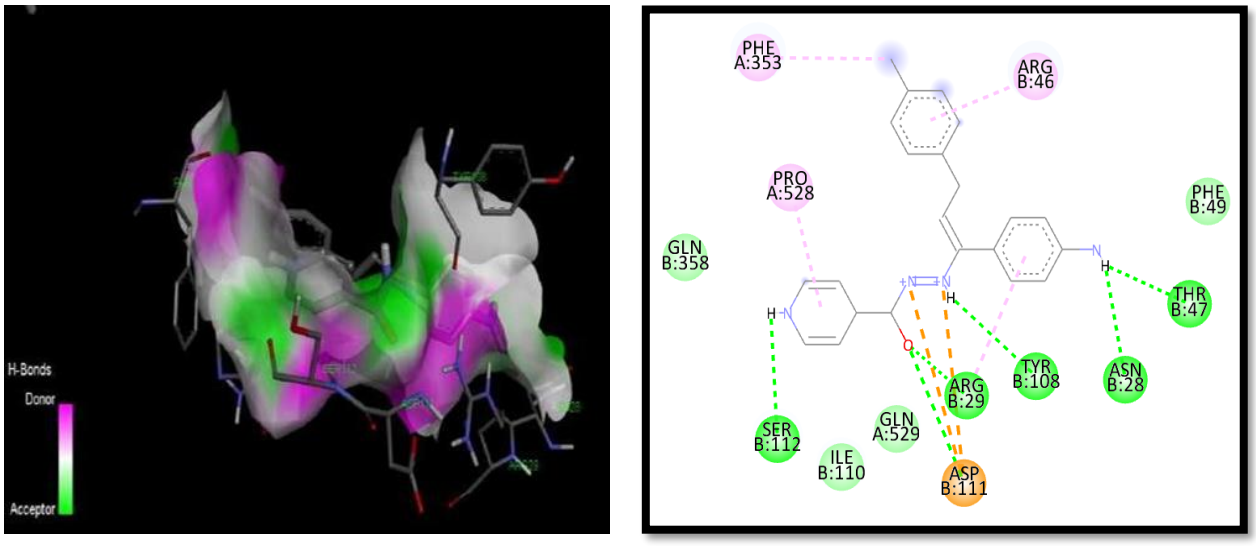

Figure 2: 3D and 2D structure of CH-9 interact with COX-2 active site

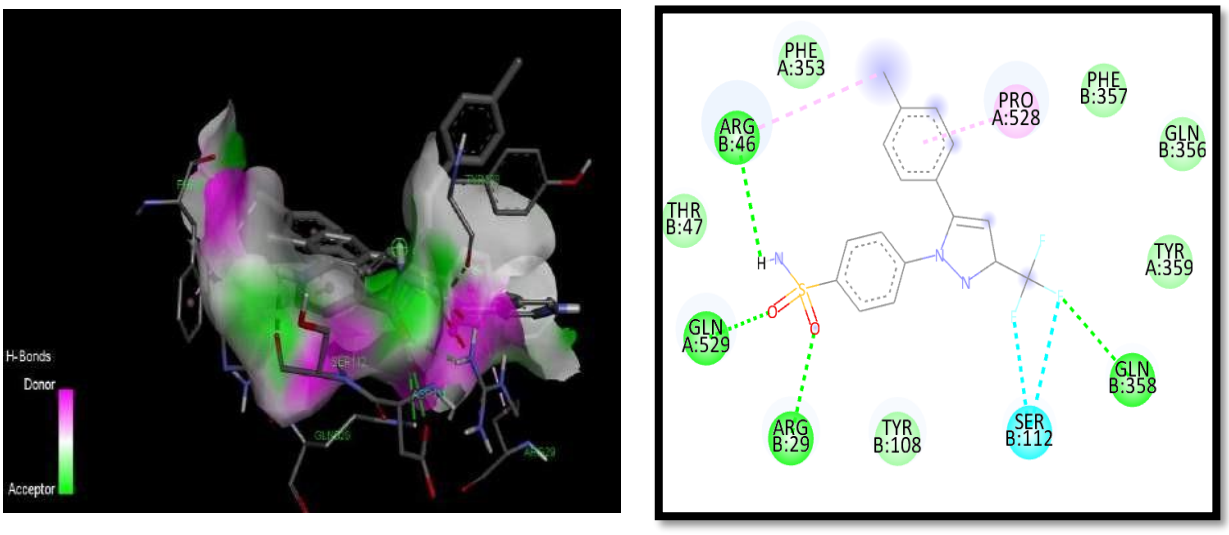

Figure 3: 3D and 2D structure of Celecoxib interact with COX-2 active site

Conclusion:

A score has been achieved by docking the thirty molecular structures of a chalcone ring derivative of chalcone hydrazide to discover the ligands that bind to the structure of the COX-2 protein. The derivative is made by combining substituted benzophenone and substituted benzaldehyde to produce substituted chalcone, which then reacted with isonicotinyl hydrazide. Thirty derivatives out performed celecoxib in terms of docking score, according to the results. It indicates that their interaction with the target protein has a higher binding energy. These substances may therefore be regarded as strong anti-inflammatory agents. To obtain anti-inflammatory activity, synthesis and in vitro testing are necessary for additional research

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