JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Molecular Docking Analysis of N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine with the SARS-CoV-2 Main Protease

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Abstract:

The emergence of COVID-19 in December 2019 unleashed a global health crisis with the novel coronavirus, SARS-CoV-2, at its epicenter. The pandemic rapidly escalated from an epidemic to a worldwide scourge, impacting over 110 million people and causing more than 2.4 million deaths by February 2021. Although significant strides have been made in vaccine development, challenges persist, including the need for multiple vaccine doses and the virus's mutational adaptability. Consequently, a surge in computer-aided drug design and discovery has unfolded, focusing on potential antiviral compounds. This study targets the Main protease (Mpro) of SARS-CoV-2, which is crucial for the virus's replication and survival. Various drugs, including known antivirals and phytochemical compounds, have been subjected to molecular docking investigations to uncover potential inhibitors. Among these, N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine stands out as a compound of interest due to its unique structural properties. Molecular docking techniques were employed to assess the potential of N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine as an inhibitor for the SARS-CoV-2 main protease. The study aims to identify novel compounds that could contribute to the ongoing fight against COVID-19 and future viral threats.

Keywords: Antiviral compounds, Main protease, Bromobenzylidene, COVID-19

1. Introduction

The emergence of COVID-19, with its origins in December 2019 in Wuhan, China, marked a significant global health crisis. The culprit behind this pandemic was identified as the novel coronavirus, SARS-CoV-2, a severe acute respiratory syndrome virus. Rapidly escalating from an epidemic to a pandemic, it has affected more than 110 million people worldwide, resulting in a staggering death toll of over 2.4 million by February 2021 [1-2].

While substantial progress has been made with large-scale clinical studies and successful distribution of mRNA, subunit, and vector vaccines, the journey has been fraught with challenges. Most COVID-19 vaccines require multiple doses, presenting logistical hurdles in administration and global distribution. Moreover, the virus's ability to mutate poses a risk to the effectiveness of certain vaccines, necessitating continuous monitoring and adaptation [2-4].

In light of these challenges, there has been a notable surge in computer-aided drug design and discovery efforts over the past year. Researchers worldwide have been engaged in extensive studies employing various docking strategies to unearth potential antiviral compounds for COVID-19. This approach holds promise in mitigating the ongoing crisis and preparing for future health threats [5-8].

SARS-CoV-2 presents a diverse array of target proteins for ligand docking, with one crucial target being the Main protease (Mpro), also known as 3-C like protease (3CLpro). Mpro plays a pivotal role in the post-translational modification of replicase polyproteins, which, in turn, are essential for processing viral proteins. This enzyme, comprising 306 amino acids, bears striking structural and sequential resemblance to the SARS-CoV-3CLpro [9]. The Mpro monomer encompasses three N-terminal domains: N-terminal domain-I, N-terminal domain-II, and N-terminal domain-III [10]. The active site of the enzyme is formed by the catalytic dyads Cys145 and His41 [11-12]. Since the onset of the pandemic, various established drugs, including HIV medications like Lopinavir and Ritonavir, as well as Peptidomimetic a-ketoamides and modified a-ketoamides inhibitors, have been subjected to docking and studied for their potential inhibitory effects on Mpro [13-17].

Docking experiments have been conducted not only on Mpro of coronaviruses but also on B coronaviruses and 3CLpro of enteroviruses. In addition to these drugs under trial, there is growing interest in evaluating antiviral phytochemical active compounds, along with the docking of numerous other compounds like flavonoids, glucosides, alkaloids, and polyphenolic substances on the SARS-CoV-2 Mpro. This extensive research aims to identify potential inhibitory activities that could pave the way for novel therapeutic drug designs [18-20].

N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine, a compound belonging to the dihydrobenzo[b][1,4]dioxin derivative family, has garnered significant attention due to its versatile pharmacological properties and potential in medicinal chemistry [21,22]. Its unique structural features, including a substituted benzylidene group and the presence of a bromine atom, render it an intriguing subject of research, offering distinct properties.

To gain a deeper understanding of this compound, it's essential to elucidate its atomic arrangement, as it holds the key to comprehending its chemical reactivity, intermolecular interactions, and potential biological activities. Within this framework, our study employs molecular docking techniques to explore the viability of N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine as a potential inhibitor for the main protease of

SARS-CoV-2. The overarching goal is to discover novel compounds that can effectively combat the SARS-CoV-2 virus.

2. Experimental section

To contribute to the global effort to combat COVID-19, numerous scientific communities are actively conducting studies on the virus. Our research employs molecular docking (MD) analysis to explore the potential antiviral properties of N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine. To pinpoint the most favorable binding sites, we conducted MD investigations using MGL tools 1.5.6 in conjunction with AutoDock Vina [23-24].

For ligand preparation, we utilized the CIF of N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine, optimizing and energy-minimizing the molecule. Additionally, we acquired the three-dimensional structure of the main protease (PDB ID: 6LU7) as a potential target for inhibiting COVID-19 from the Protein Data Bank. Preparing the protein structure involved the removal of water and the N3 inhibitor [25], followed by the addition of nonpolar hydrogen atoms and energy minimization using AutoDock Tools.

To define the atomic potential binding site, we set a grid size of x = -11.575, y = 14.611, and z = 65.164. Our analysis yielded a negative binding affinity score in kcal/mole units for N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine. To gain insight into ligand interactions, we visualized and examined the results using the Biovia Discovery Studio 2019 visualizer [26].

3. Results and discussion

The properties of the optimal docking pose for N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine were thoroughly examined, with a focus on its binding pocket within the main protease (6LU7), contrasting it with the binding mode of the N3 inhibitor in the active site. The binding interactions were scrutinized, shedding light on the molecular basis of the compound's binding to the main protease.

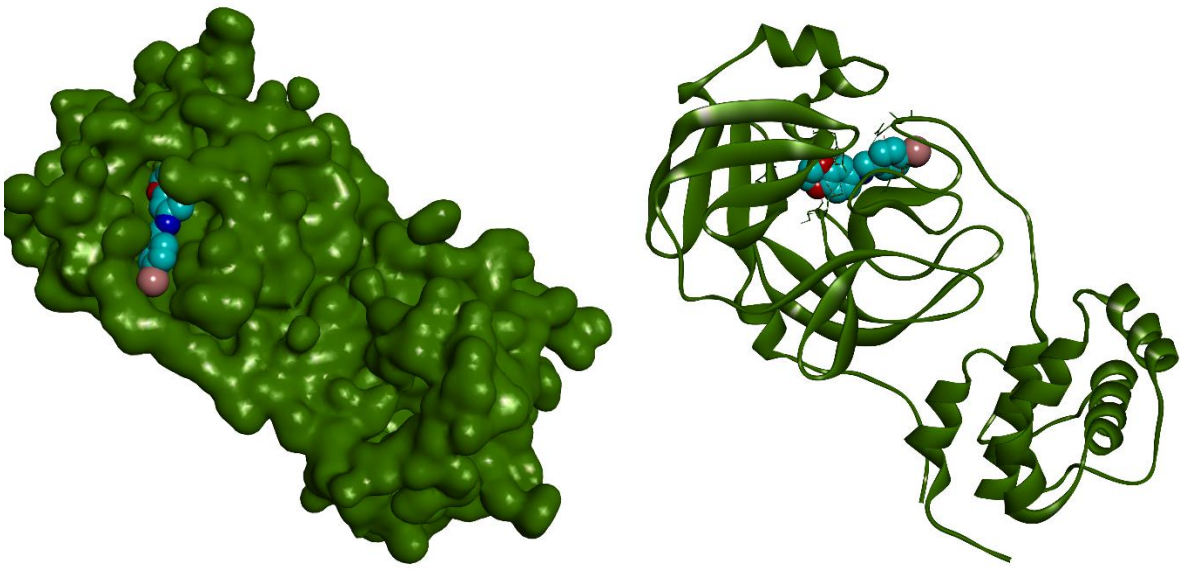

Figure 1: Glide docking of N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine into the active pocket of protease of covid-19. Surface (left) and cartoon (right) representation of docked confirmation.

In the active site of the main protease, the N3 inhibitor establishes critical connections through both hydrophobic and hydrogen bond interactions with the catalytic dyad comprising CYS-145 and HIS-41. This interaction is crucial for the inhibitor's inhibitory effect on the main protease.

Detailed analysis of the molecular docking results revealed the involvement of residues CYS-145 and HIS-41 in the binding of N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine to the main protease. HIS-41 forms hydrogen bonds with the oxygen atom and centroid of the dioxin ring, contributing to the stability of the binding. Meanwhile, CYS-145 residue engages in pi-alkyl and pi-donor hydrogen bonds with the dioxin and amine rings, further anchoring the ligand within the active site.

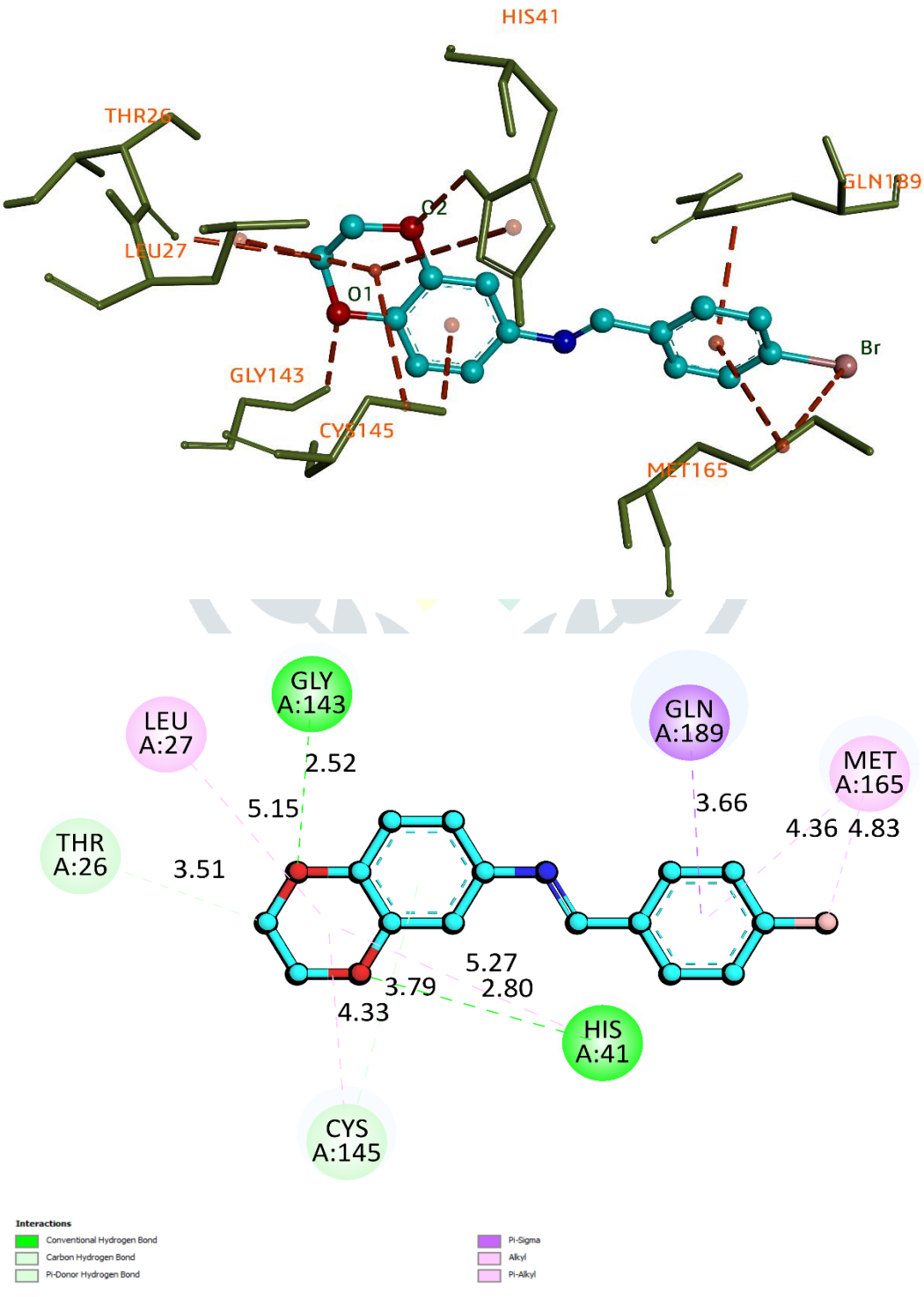

Figure 2: Interaction between N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine and 6LU7

protein.

The main protease's active pocket was shown to have a strong affinity for N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine, forming several conventional hydrogen bonds with a binding energy of -6.5 kcal/mol. These interactions with various residues, including GLY143, HIS-41, CYS-145, LEU27, MET165, GLN189, THR26, and CYS145, encompass conventional hydrogen bonds, van der Waals forces, carbon hydrogen bonds, pi-donor hydrogen bonds, pi-sigma interactions, Alkyl bonds, and pi-alkyl interactions. This diverse array of binding interactions highlights the compound's strong and multi-faceted affinity for the main protease, shedding light on its potential as an inhibitor. 2).

4. Conclusion

The research findings shed light on the molecular interactions between N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine and the SARS-CoV-2 main protease. In-depth analysis of the docking results revealed that the compound exhibited a strong binding affinity within the active pocket of the main protease, forming several conventional hydrogen bonds with a binding energy of -6.5 kcal/mol. The interactions involved key residues, including GLY143, HIS-41, CYS-145, LEU27, MET165, GLN189, THR26, and CYS145, encompassing various interaction types such as conventional hydrogen bonds, van der Waals forces, carbon hydrogen bonds, pi-donor hydrogen bonds, pi-sigma interactions, Alkyl bonds, and pi-alkyl interactions. Notably, CYS-145 and HIS-41 played vital roles in establishing the binding of N-(4-Bromobenzylidene)-2,3-dihydrobenzo[b][1,4]dioxin-6-amine to the main protease. These results underscore the compound's potential as an inhibitor for the SARS-CoV-2 main protease, offering a promising avenue for the development of novel therapeutic agents in the ongoing battle against COVID-19 and future viral challenges.

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