Evaluating the Inhibitory Potential: Molecular Docking of 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one against SARS-CoV-2 Main Protease

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Abstract:

In response to the global challenge posed by the COVID-19 pandemic, extensive research efforts are underway to identify potential antiviral agents. This study employed molecular docking analysis to investigate the binding properties of 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one, a chemical compound, against the main protease (6LU7) associated with the COVID-19 virus. The ligand and protein were prepared, and molecular docking was performed to assess the binding affinity of the compound. The results revealed multiple binding interactions, including hydrogen bonds and hydrophobic interactions, highlighting the strong affinity of 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one for the main protease. This research contributes to the ongoing efforts to discover potential antiviral agents for COVID-19.

Keyworsds: COVID-19, Main Protease, Mesityl, Thiophen,

1. Introduction

The advent of COVID-19, which emerged in December 2019 in Wuhan, China, signified a major global health emergency. This pandemic was triggered by the novel coronavirus, SARS-CoV-2, a virus responsible for severe acute respiratory syndrome. Progressing swiftly from an epidemic to a global pandemic, it has impacted over 110 million individuals globally, leading to a devastating death toll exceeding 2.4 million by February 2021 [1-2].

Despite significant advancements achieved through extensive clinical trials and the successful deployment of mRNA, subunit, and vector vaccines, the path has been marred by difficulties. Many COVID-19 vaccines mandate multiple doses, introducing logistical complexities in their delivery and worldwide distribution. Furthermore, the virus's capacity to undergo mutations poses a potential threat to the efficacy of specific vaccines, underscoring the need for ongoing vigilance and adjustment [2-4].

Given these hurdles, there has been a remarkable upsurge in computer-assisted drug design and discovery initiatives in the last year. Researchers across the globe have been deeply immersed in comprehensive investigations, utilizing diverse docking techniques to unearth prospective antiviral agents for combating

COVID-19. This method offers hope in addressing the ongoing crisis and fortifying our readiness for potential future health challenges. [5-8].

SARS-CoV-2 offers a wide range of target proteins suitable for ligand docking, and among them, the Main protease (Mpro), also referred to as 3-C like protease (3CLpro), stands out as a crucial target. Mpro plays a central role in the post-translational modification of replicase polyproteins, a process vital for the maturation of viral proteins. Remarkably, this enzyme, consisting of 306 amino acids, shares a significant structural and sequential similarity with the SARS-CoV-3CLpro [9].

The Mpro monomer consists of three distinct N-terminal domains: N-terminal domain-I, N-terminal domain-II, and N-terminal domain-III [10]. The enzyme's active site is created by the catalytic pair Cys145 and His41 [11-12]. Since the beginning of the pandemic, a range of established drugs, including HIV medications like Lopinavir and Ritonavir, as well as Peptidomimetic a-ketoamides and modified a-ketoamides inhibitors, have undergone docking studies to explore their potential for inhibiting Mpro [13-17].

Docking investigations have extended beyond the Mpro of coronaviruses to encompass B coronaviruses and 3CLpro of enteroviruses. Alongside the drugs currently undergoing trials, there is a mounting enthusiasm for assessing the antiviral properties of phytochemical compounds. Furthermore, numerous other compounds, including flavonoids, glucosides, alkaloids, and polyphenolic substances, have been subjected to docking studies involving the SARS-CoV-2 Mpro. This comprehensive research endeavor seeks to uncover potential inhibitory effects that could serve as a foundation for pioneering therapeutic drug design [18-20]. Chalcones, also known as 1,3-diphenylprop-2-ene-1 compounds, belong to the category of organic compounds characterized by the presence of two aromatic rings combined with an unsaturated ketone functional group. Owing to their intriguing biological properties, these compounds are now recognized as valuable candidates in various pharmaceutical and medicinal chemistry applications, holding promise for future developments in the field [21,22].

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 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one 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 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one. 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 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one, 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 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one. To gain insight into ligand interactions, we visualized and examined the results using the Biovia Discovery Studio 2019 visualizer [26].

3. Results and discussion

A comprehensive analysis was conducted on the optimal docking position of 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one, with particular attention to its interaction with the binding pocket of the main protease (6LU7). This was compared to the binding mode of the N3 inhibitor in the active site. The study delved into the binding interactions, providing insights into how the compound binds to the main protease. Within the main protease's active site, the N3 inhibitor forms vital connections through both hydrophobic and hydrogen bond interactions with the catalytic dyad consisting of CYS-145 and HIS-41. This interaction is instrumental in the inhibitor's inhibitory effect on the main protease.

The active site of the main protease exhibited a notable attraction to 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one, establishing multiple traditional hydrogen bonds with a binding energy of -6.8 kcal/mol. These interactions involved various active site residues, including HIS-41, CYS-145, LEU27, HIS-163, and SER1444, encompassing traditional hydrogen bonds, pi-donor hydrogen bonds, pi-sigma interactions, Pi-Sulfur and Pi-Pi T-shaped interactions, as well as pi-alkyl interactions

A detailed examination of the molecular docking outcomes unveiled the pivotal role played by residues CYS-145 and HIS-41 in the binding of 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one to the main protease. HIS-41 engages in Pi-Sulfur and Pi-Pi T-shaped interactions with the sulfur atom and the centroid of the thiophene ring, maintaining distances of 5.78 Å and 5.11 Å, respectively, thereby bolstering the stability of the protein-ligand connection. Simultaneously, the CYS-145 residue participates in a conventional hydrogen bond interaction with the oxygen atom (C=O) at a distance of 2.27 Å, firmly anchoring the ligand within the active site of the main protease. These diverse forms of binding interactions underscore the compound's robust and multifaceted affinity for the main protease, shedding light on its potential as an inhibitor.
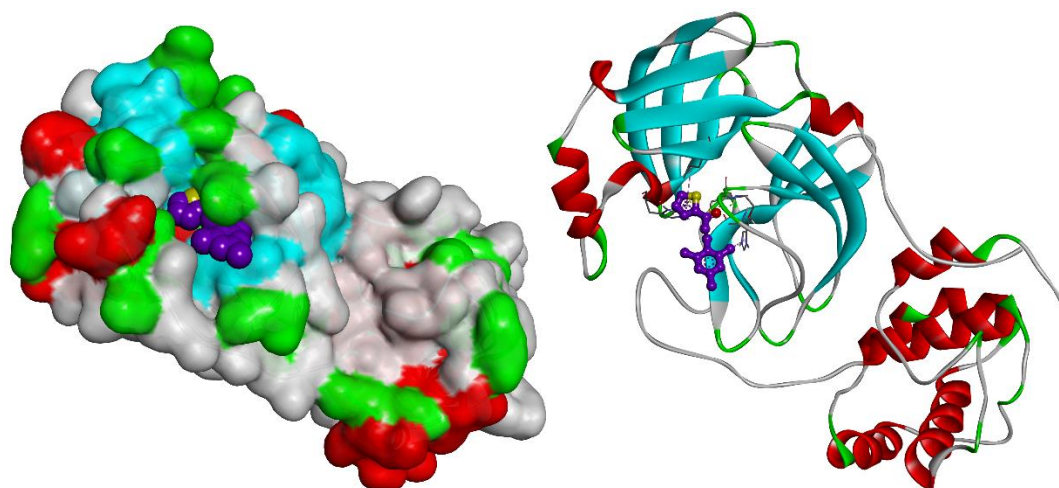

Figure 1: Glide docking of 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one into the active pocket of protease of

covid-19. Surface (left) and cartoon (right) representation of docked confirmation.
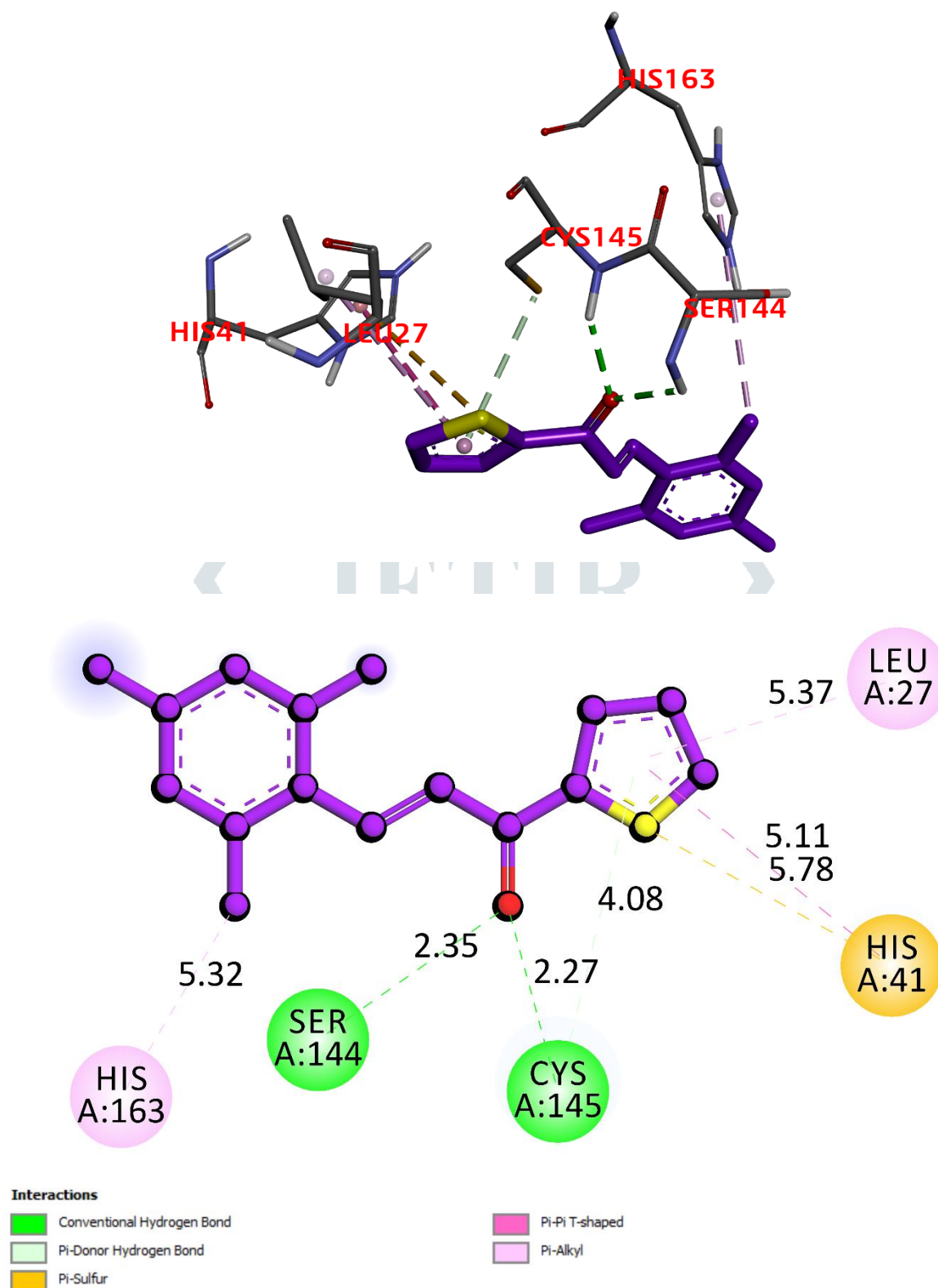

Figure 2: Interaction between 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one and 6LU7 protein.

Conclusion

In this experimental study, we conducted molecular docking analysis to explore the potential of 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one as an antiviral agent against the main protease (6LU7) associated with COVID-19. The results of our analysis revealed a significant binding affinity of the compound for the main protease, with a binding energy of -6.5 kcal/mol. Multiple binding interactions were identified, including conventional hydrogen bonds, pi-donor hydrogen bonds, pi-sigma interactions, Pi-Sulfur, Pi-Pi T-shaped, and pi-alkyl interactions. Notably, residues CYS-145 and HIS-41 played a crucial role in stabilizing the protein-ligand

complex through various interactions.

These findings provide valuable insights into the potential of 3-mesityl-1-(thiophen-2-yl)prop-2-en-1-one as an inhibitor for the main protease of the COVID-19 virus. The compound's diverse array of binding interactions underscores its multi-faceted affinity for the main protease, which is vital for inhibiting the virus's replication. This research contributes to the ongoing global efforts to identify and develop effective antiviral agents against COVID-19, and further studies are warranted to validate the compound's inhibitory potential through in vitro and in vivo experiments.

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