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A Molecular Docking Study: Benzoxazolone Derivatives against SARS-CoV-2 Omicron Subvariant EG.5.1

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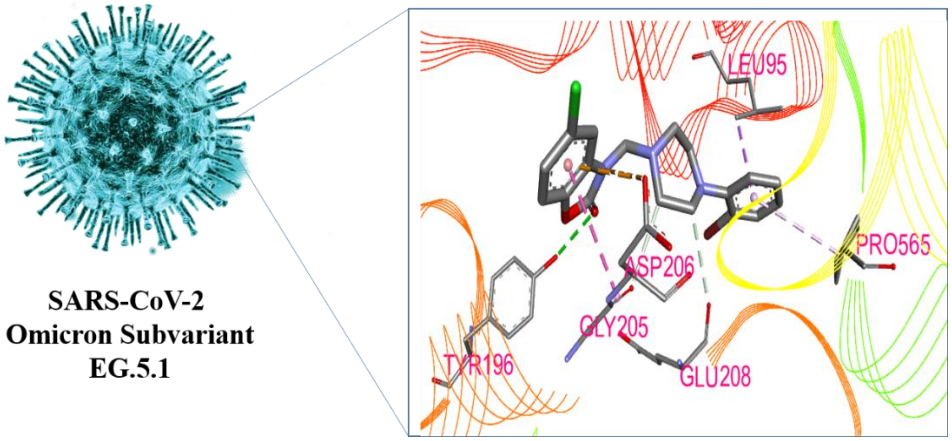
ABSTRACT

In the ongoing COVID-19 pandemic, it is important to develop treatment strategies and new drug candidates that target the interactions between the receptor-binding domains (RBDs) of the currently circulating SARS-CoV-2 Omicron subvariants-XBB.1.5 and EG.5.1 and the human ACE2 receptor. The SARS-CoV-2 Omicron subvariant EG.5.1, currently in circulation, possesses a faster transmission capability compared to other subvariants. It weakens the neutralizing effect of existing monoclonal antibodies and evades vaccine-generated antibodies. Thus, there is a need for new molecules that can target EG.5.1 RBD. In this study, the effectiveness of (8 Compounds) derivatives containing benzoxazolone and piperazine rings, which have previously been reported to have antiviral properties, against XBB.1.5 and EG.5.1 RBDs, was measured using molecular docking, molecular dynamics simulation, and MM-PBSA methods. For the *in silico* study, AutoDock Vina, Discovery Studio Visualizer, and GROMACS molecular dynamics software were utilized. According to the results, the compounds were found to be effective against the EG.5.1 Omicron subvariant. Among the tested compounds, *5-chloro-3-[4-(2-bromophenyl)piperazin-1-ylmethyl]benzoxazol-2-one* (Compound 8) had the highest affinity and binding energy values for both XBB.1.5 and EG.5.1 RBDs. In conclusion, the development of Mannich bases containing benzoxazolone and piperazine ring systems will be beneficial against both EG.5.1 and future variants of concern.

GRAPHICAL ABSTRACT



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Introduction

SARS-CoV-2, the virus responsible for COVID-19, is constantly evolving, leading to the emergence of new variants such as Omicron, which is currently dominant worldwide [1]. Furthermore, the continuous mutation of the Omicron resulted in the subvariants evolution, including BA.1, BA.2, BA.5, BQ.1, and XBB.1.5. The XBB.1.5 variant is currently the most dominant variant globally among all the variants [2]. Several Omicron sublineages emerged, including EG.5.1, now prevalent. In contrast with previous subvariants, subvariant EG.5.1 had additional mutations in the receptor-binding domain (RBD) that accelerated transmission, eventually becoming predominant in human societies. The RBD of the spike protein in SARS-CoV-2 plays a crucial role in binding to the host cell's ACE2 receptor. Mutations in the RBD can alter the interactions between the virus and the host cell, affecting the virus's ability to enter and infect the host cell. Certain mutations in the RBD can lead to an increased binding affinity between the spike protein and the ACE2 receptor. This enhanced binding affinity can facilitate more efficient viral entry into host cells, potentially increasing viral replication and transmission. Some mutations in the RBD may affect the virus's interaction with the host immune system. This can lead to immune evasion, where the virus becomes less susceptible to neutralization by antibodies, either from prior infection or vaccination. As a result, the virus can evade the host's immune response and continue to replicate and transmit [3]. The interaction between the RBDs of coronaviruses and host receptors provides a structural framework for investigating molecular-level changes occurring over time. As is well known, SARS-CoV-2 uses the Angiotensin-converting enzyme 2 (ACE2) receptor for cellular entrance [4]. Mutational variations in the RBDs of different variants of SARS-CoV-2 affect the binding affinity with ACE2. Besides, genetic mutations lead to variations in infectiousness of different SARS-CoV-2 variants [5].

Currently, there has been a discernible escalation in the worldwide prevalence of the XBB. 1.5 sub-variant, which originates from the Omicron variant of SARS-CoV-2 [6]. The EG.5.1 variant has become a significant genetic variation in this context. In contrast to XBB.1.5, the EG.5.1 variant harbors additional mutations in the S glycoprotein, namely, F456L and Q52H [7]. Nevertheless, the transmissibility, pathogenicity, and potential for immune evasion associated with the EG.5.1 variant remains relatively limited. It has been reported that the EG.5.1 variant is more prevalent than XBB.1.5, possibly due to changed antigenic characteristics and enhanced transmissibility [8]. Therefore, a notable concern revolves around the impact of variations in the receptor binding sites of Omicron subvariants on the drugs efficacy designed to target these specific locations. Variations in the RBD can result in changes to the spike protein's structure. These changes can affect the binding affinity between the spike protein and its target receptor, such as the human ACE2 receptor. When drugs or antibodies are designed to target specific regions on the spike protein, alterations in these regions can affect the binding affinity. Some RBD variations may lead to the virus evading the host's immune system more effectively. This can occur when the virus acquires mutations that reduce its susceptibility to neutralization by antibodies. As a result, drugs or antibodies that were effective against the original virus strain may become less effective against variants with these RBD mutations.

In drug design, nitrogen-containing ring systems with different pharmacological activities are commonly used [9]. Benzoxazolones are also among the ring systems with broad pharmacological activity [10-19]. Research conducted on benzoxazole ring systems includes derivatives obtained from the 2nd, 3rd, 5th, and 6th ring positions [10]. Studies indicate that structures containing a heterocyclic core can exhibit effective antiviral properties [20]. According to recent research, benzoxazole derivatives also exhibit inhibitory effects against HIV (Human Immunodeficiency Virus) [20]. Besıdes benzoxazole, the 4-substituted piperazine ring is also found in the structure of

organic molecules with antiviral effects [21]. Moreover, Mannich bases are chemical compounds that have antiviral activity [22]. Mannich bases typically possess structural features that can be included in various compound classes aimed at drug development [23]. Therefore, research on the structures and properties of specific Mannich bases is necessary to evaluate whether they have antiviral effects. Mannich bases with antiviral effects have been an interesting topic in research, and some Mannich bases are effective against certain types of viruses [24]. The Mannich reaction is used for the synthesis of Mannich bases. The Mannich reaction results from the reaction of a carbonyl compound (aldehyde or ketone) with an amine and an acetyl compound [25]. Mannich bases are compounds with different organic groups and play a significant role in drug development, peptide synthesis, natural product synthesis, and various other chemical synthesis fields. Mannich bases have been known to possess antiviral activity against various viruses. In this study, the authors aim to explore whether Mannich bases, specifically those containing benzoxazolone and piperazine ring structures, can exhibit antiviral properties against the SARS-CoV-2 Omicron subvariants, including EG.5.1. Investigating the antiviral potential of these compounds is particularly relevant in the context of the COVID-19 pandemic. Mannich bases are versatile compounds with a wide range of pharmacological activities. They are commonly used as intermediates in drug development. Given the need for effective drugs and therapeutics to combat SARS-CoV-2 and its variants, exploring Mannich bases as potential drug candidates is a relevant avenue of research. Mannich bases, like other chemical compounds, may exhibit antiviral effects through various mechanisms, such as inhibiting viral entry into host cells, disrupting viral replication, or interfering with viral protein function. Understanding the mechanisms of action is essential for developing targeted antiviral strategies. [23]. The Mannich reaction is a widely employed method for the formation of new carbon-carbon and carbon-nitrogen bonds and is one of the fundamental reactions in organic chemistry. This reaction finds applications in various biological and chemical processes [26].

In light of all this information, attempting to achieve a synergistic effect by combining benzoxazolone and piperazine ring structures that play a role in antiviral activity using the Mannich reaction can be effective in designing and synthesizing new antiviral derivatives. Furthermore, in silico methods such as molecular docking provide preliminary data in determining the activity and possible mechanism of potential drug candidates before *in vivo* and *in vitro* experiments. As part of this study, a molecular docking investigation was carried out concentrating on the crystallographic structures of the RBDs of two recently discovered SARS-CoV-2 Omicron subvariants, XBB.1.5 and EG.5.1. The study involved the combination of previously synthesized several Mannich bases of 3-substituted benzoxazolones including piperazine moieties [27].

The main aim of this study was to elucidate the binding interactions and possible mechanisms of action of SARS-CoV-2 Omicron sub-variants and potential drug candidates with benzoxazolone structure known to have antiviral effects.

Experimental

Selection of protein targets and modeling

Before analysis, SARS-CoV-2 XBB.1.5 Omicron RBD complex (PDB: 8SPI) was downloaded from the Protein Data Bank in PDB file format. Mutations in the genetic code of the spike protein for SARS-CoV-2 XBB.1.5 and EG.5.1 sub-variants were screened using the GISAID database (https://gisaid.org/), and mutation site differences between the variants were compared. The genetic sequence regions that underwent mutation in XBB.1.5, as compared to BA.5, were identified. Comparative modeling was performed with the Modeller program [28], and the three-dimensional (3D) structure for the EG.5.1 variant was extracted.

Preparation of dataset and molecular docking

Before the docking procedure, previously synthesized 3-substituted benzoxazolone derivatives; *5-chloro-3-(1-piperonylpiperazin-1-ylmethyl)benzoxazol-2-one* (1), *3-[4-(2-ethylbenzyl)piperazin-1-ylmethyl]benzoxazol-2-one* (2), *5-chloro-3-[4-(2-ethylbenzyl)piperazin-1-ylmethyl]benzoxazol-2-one* (3), *5-chloro-3-[4-(4-hydroxyphenyl)piperazin-1-ylmethyl]benzoxazol-2-one* (4), *3-(4-cyclopropylpiperazin-1-ylmethyl)benzoxazol2-one* (5), *5-chloro-3-(4-cyclopropylpiperazin-1-ylmethyl)benzoxazol-2-one* (6), *3-[4-(2-bromophenyl)piperazin-1-ylmethyl]benzoxazol-2-one* (7), and *5-chloro-3-[4-(2-bromophenyl)piperazin-1-ylmethyl]benzoxazol-2-one* (8) were selected as ligands [18].

The two-dimensional (2D) representations of the selected ligands were obtained using ChemDraw Pro 12.0 software. The ligands were subsequently extracted and converted into mol2 files using LigandScout 4.4.5 software, a preparatory step for molecular docking. Before initiating the molecular docking process, meticulous refinement was conducted on both the three-dimensional (3D) molecular structures of the ligands and the RBDs of XBB.1.5 and EG.5.1, as targets. In this refinement procedure, all water molecules and heteroatoms were eliminated. Subsequently, polar hydrogens were added, and Gasteiger charges were computed to enhance accuracy.

Following this structural refinement, the 3D conformations of XBB.1.5 and EG.5.1 were saved as a PDBQT file. For the subsequent molecular docking analysis, AutoDock Vina and Discovery Studio Visualizer programs were employed to facilitate the extraction of diverse docking poses, as well as the calculation of binding affinities (ΔG) and the generation of ligand-receptor interaction profiles for the selected ligands. Consistency was maintained throughout all docking procedures by employing a grid box with dimensions of 32 × 32 × 32 Å.

Molecular dynamics simulation

Molecular dynamics simulations were carried out using the GROMACS molecular dynamics software. The GROMOS96 force field parameters were applied to simulate the protein-ligand complexes. The overall charge neutrality of the protein-ligand complex was maintained by sodium (Na^+) and chloride (Cl^-) ions. In addition, a simplified point-charge water model was employed to mimic water molecules. The simulations were conducted under conditions of 310 K temperature and 1 bar pressure, lasting for a duration of 100 nanoseconds. This simulation procedure adhered to a previously documented methodology [29]. During the simulations, we observed the interactions between the protein and ligand and evaluated root-mean-square deviation (RMSD) characteristics to identify the most favorable conformations. A common temperature for simulating biological systems is 300-310 Kelvin (K), which is approximately room temperature. Molecular dynamics simulations can be performed under constant pressure conditions, typically around 1 bar (approximately 100 kPa), to simulate systems at standard atmospheric pressure.

MM-PBSA calculations

Molecular Mechanics/Position-Boltzmann Surface Area (MM-PBSA) method to determine the binding free energies for all RBD-ligand complexes [30]. The binding free energies were calculated using a previously published procedure [31]. The free energies of protein-ligand complexes are displayed as:

$\Delta G_{bind} = \Delta G_{complex} - (\Delta G_{protein} + \Delta G_{ligand})$

The terms ΔG_{bind}, $\Delta G_{complex}$, $\Delta G_{protein}$, and ΔG_{ligand} represent the binding energy, complex energy, protein energy, and ligand energy in a solvent, respectively. The binding free energy values were calculated using the molecular dynamics simulation period of 70-100 ns, during which the complexes remained stable without fluctuations.

Table 1: The binding affinity values of tested benzoxazolone derivatives (ligands) against receptor binding domain of XBB.1.5 and EG.5.1, ΔG (kcal/mol)

Ligands	Binding Affinity, ΔG (kcal/mol)	
	XBB.1.5	EG.5.1
Compound 1	-6.4	-7.0
Compound 2	-6.9	-7.1
Compound 3	-7.0	-7.8
Compound 4	-7.1	-8.0
Compound 5	-7.5	-8.1
Compound 6	-7.8	-8.3
Compound 7	-8.0	-8.6
Compound 8	-8.2	-8.9

Results and Discussion

In this study, the activity of selected 3-substituted benzoxazolone derivatives was tested on the XBB.1.5 and EG.5.1 RBDs. The binding affinity values for all resulting complexes were observed to range from -6.4 to -8.9 kcal/mol. Overall, surprisingly, all compounds exhibited stronger binding affinities in the EG.5.1 RBD region compared to XBB.1.5. Among all compounds, Compound 8 (-8.2 kcal/mol; XBB.1.5, -8.9 kcal/mol; EG.5.1), Compound 7 (-8.0 kcal/mol; XBB.1.5, -8.6 kcal/mol; EG.5.1), and Compound 6 (-7.8 kcal/mol; XBB.1.5, -8.3 kcal/mol; EG.5.1) showed the strongest binding affinities, respectively. The binding affinity values of all tested compounds against the SARS-CoV-2 Omicron subvariants XBB.1.5 and EG.5.1 RBD regions were summarized in Table 1.

In addition to molecular docking, the molecular dynamics simulation study revealed that all ligands maintained their complexes' stability with the XBB.1.5 and EG.5.1 RBD regions during the last 30 seconds of the 100 ns simulation period. Consequently, the binding energy values of the complexes were measured using MM-PBSA calculations over the final 30 ns time frame. The binding energies of the ligands are presented in Table 2.

According to the results, similar to the findings in the molecular docking method, Compound 8, Compound 7, and Compound 6 displayed stronger binding energies on the EG.5.1 RBD region. The binding energy of Compound 8 was calculated as -215.47 ± 3.36 kJ mol^{-1} for XBB.1.5 and -281.16 ± 3.12 kJ mol^{-1} for EG.5.1. Compound 7 exhibited binding energies of -181.73 ± 2.47 kJ

Table 2: The calculated MM-PBSA values of tested benzoxazolone derivatives (ligands) with receptor binding domain complexes, (kJ mol^{-1})

Ligands	MM-PBSA Binding Energy (kJ mol^{-1})	
	XBB.1.5 RBD-ligand complex	EG.5.1 RBD-ligand complex
Compound 1	-116.63± 2.28	-154.41± 2.25
Compound 2	-123.42± 2.21	-156.14± 3.13
Compound 3	-131.19± 3.32	-167.02± 3.25
Compound 4	-149.35± 4.23	-172.72± 2.57
Compound 5	-153.46± 2.36	-187.54± 3.16
Compound 6	-164.52± 3.38	-191.38± 2.54
Compound 7	-181.73± 2.47	-218.28± 2.73
Compound 8	-215.47± 3.36	-281.16± 3.12

mol^{-1} for XBB.1.5 and -218.28 ± 2.73 kJ mol^{-1} for EG.5.1, while Compound 6 showed -164.52 ± 3.38 kJ mol^{-1} for XBB.1.5 and -191.38 ± 2.54 kJ mol^{-1} for EG.5.1. Among the tested compounds, Compound 1 had the lowest binding affinities for both the XBB.1.5 and EG.5.1 RBD regions with values of -6.4 and -7.0 kcal/mol, respectively. Similarly, Compound 1 was determined as the least effective compound with binding energy values of -116.63 ± 2.28 kJ mol^{-1} for XBB.1.5 and -154.41 ± 2.25 kJ mol^{-1} for EG.5.1 variants.

As of January 2023, the XBB.1.5 subvariant of SARS-CoV-2 is rapidly increasing in prevalence and dominance in certain countries [32]. XBB.1.5 has various mutations that make it more efficient in binding to the ACE-2 receptor [33]. On the other hand, the EG.5.1 lineage of SARS-CoV-2, also referred to as Eris, has been spreading worldwide since May 2023, and it gained recognition as a variant of concern by the World Health Organization (WHO) [34]. Some literature studies also demonstrated the immune evasion capabilities of the XBB.1.5 and EG.5.1. According to these studies, EG.5.1 was found to escape neutralizing monoclonal antibodies (mAbs) better than previous SARS-CoV-2 lineages [35]. All of these findings continue to raise significant concerns about the efficacy of both the current monoclonal antibodies and vaccines used in COVID-19 treatment.

In the literature, an assessment of the immune system's response to the EG.5.1 variant was recently undertaken. This evaluation involved conducting tests to determine its neutralization potential, employing serum samples obtained from individuals who had received mRNA-based vaccines [36]. The XBB.1.5 and XBB.1.9.2 strains of SARS-CoV-2 were also included in comparative investigations, which were done to clarify the consequences of mutations unique to the EG.5.1 variant. In conclusion, earlier research has shed light on several important EG.5.1 features. When tested in naive wild-type hamsters, it was discovered that EG.5.1 displays a proliferation rate similar to that of XBB.1.5, but with comparatively greater transmissibility [37]. Furthermore, since EG.5.1 was found in the nasal and pulmonary tissues of infected hamsters, the viral tropism of this variant is different from the XBB.1.5 variant after airborne transmission. While immune evasion was present in EG.5.1, it was substantially more effective than both XBB.1.5 and XBB.1.9.2 variations in this respect [38].

Computer-aided drug design and analysis is a valuable tool for exploring mutations in SARS-CoV-2 variants and their impact on mutant proteins [39]. Many therapeutic strategies for addressing COVID-19 involve preliminary *in silico* research. As the Omicron subvariants of SARS-CoV-2 increase, there is a growing trend in computer-aided investigations to develop new drug candidates, analyse monoclonal antibodies, and assess the effectiveness of vaccines against viral infections [40]. Crucial for understanding changes in binding energies of ligands and modified viral proteins, molecular docking, and simulation studies using mutated SARS-CoV-2 S protein structures are on the rise [40]. In another *in silico* study, a conservation analysis of the SARS-CoV-2 spike protein sequence. This research also compared the binding energies of ACE2 with interactions involving mutated and non-mutated spike proteins using molecular docking through the ClusPro online server. The findings indicated that the L5f and P1263l mutation sites and the non-mutated spike protein showed similar docking scores [38]. Previous research has demonstrated that molecular docking is a highly effective approach for assessing interactions between various SARS-CoV-2 targets and ligand complexes, as well as the impact of mutations on these complex structures.

In this study, we conducted amino acid interaction analyses after molecular docking in both 2D and 3D formats. We focused on the analysis of amino acid sequences within the RBD region of the common variant EG.5.1, which is believed to play a significant role in ACE2 receptor binding. This analysis was performed on Compound 8, Compound 7, and Compound 6, the most active compounds identified in our molecular docking and simulation study.

The results indicate that the tested compounds exhibited interactions with active amino acid residues in the EG.5.1 RBD region through Pi-Sigma, Pi-Anion, and attractive charge interactions involving the benzoxazolone ring. In addition, carbon-hydrogen bond interactions were observed through the piperazine ring in the main structure of the compounds. Detailed graphs illustrating the amino acids with which the tested derivatives interacted at the EG.5.1 binding sites are provided in Figures 1-4.

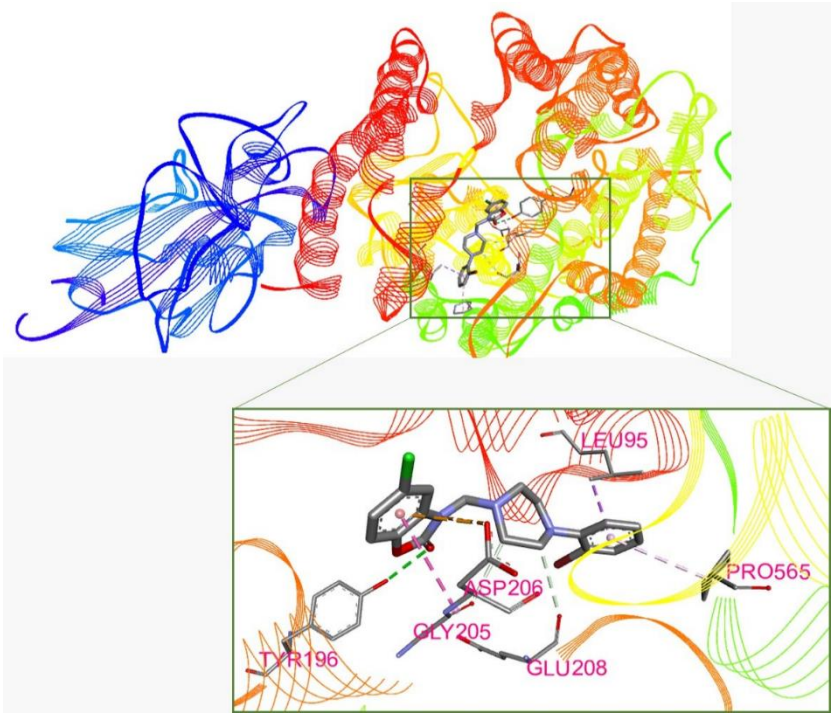

Figure 1: The 3D amino acid interactions of compound 8 in the receptor binding domain of EG.5.1

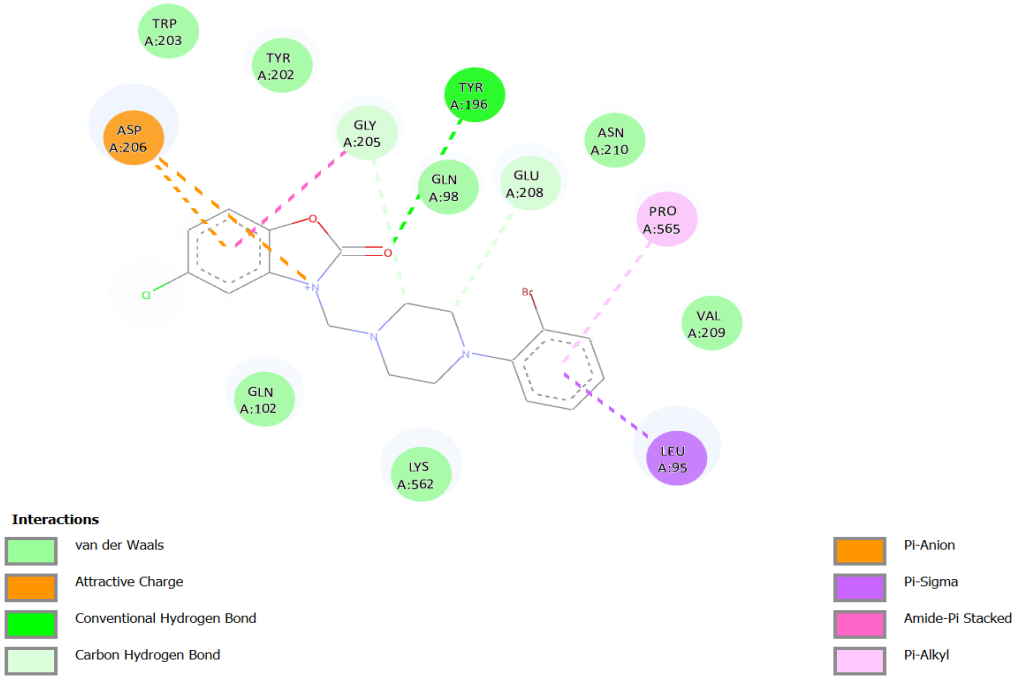

Figure 2: The 2D amino acid interactions of compound 8 in the receptor binding domain of EG.5.

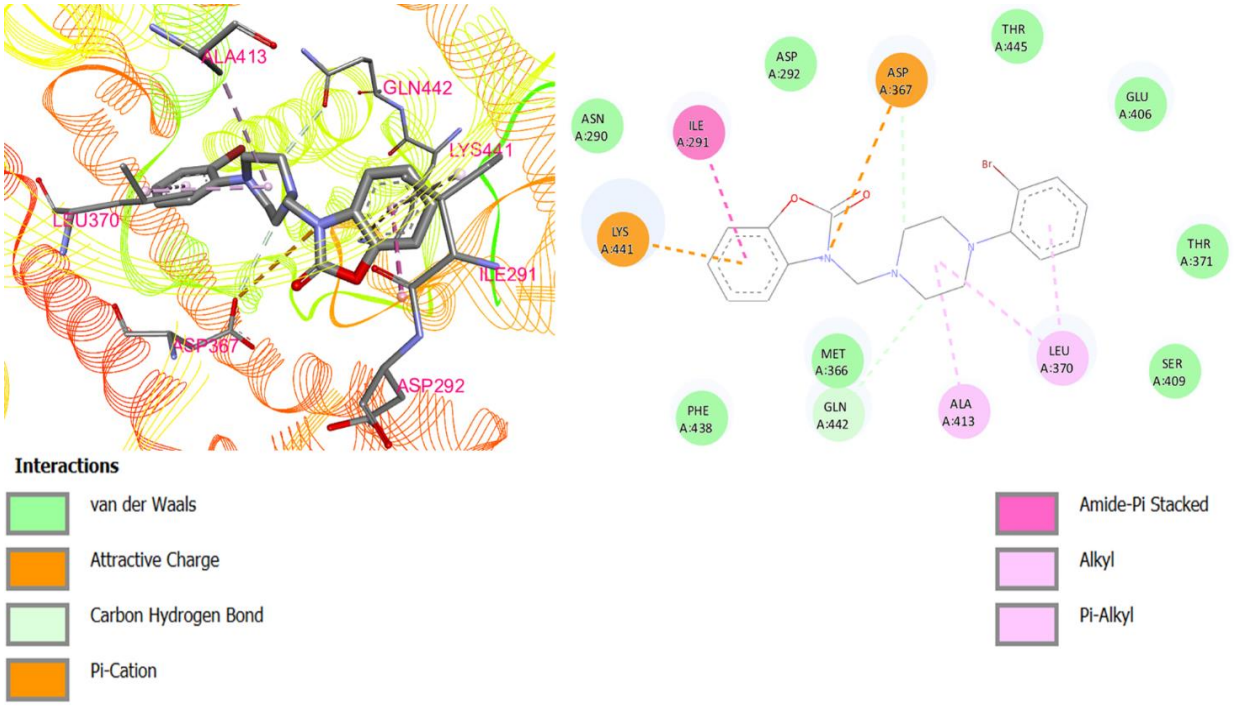

Figure 3: The 2D amino acid interactions of compound 7 in the receptor binding domain of EG.5.1

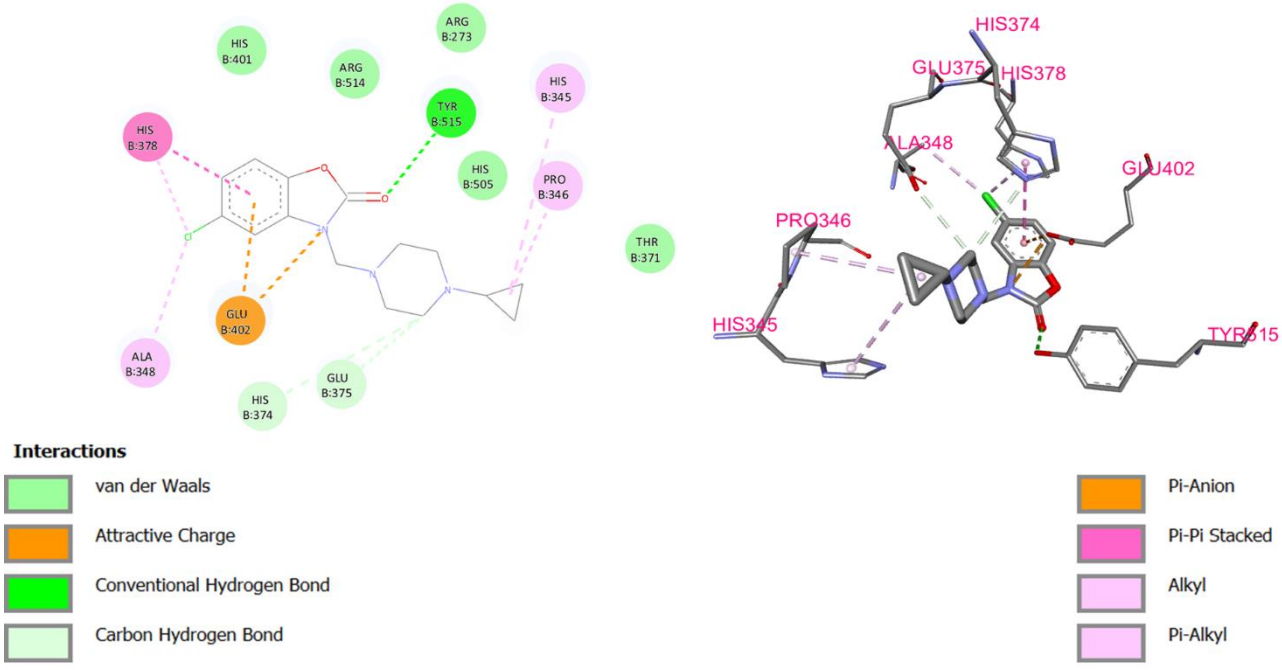

Figure 4: The 2D and 3D amino acid interactions of compound 6 in the receptor binding domain of EG.5.1

Conclusion

This study compared the amino acid sequences that make up the RBD binding regions for the SARS-CoV-2 Omicron sub-variants, XBB.1.5 and EG.5.1, and demonstrated that 3-substituted benzoxazolone derivatives could be effective against both variants. Given the widespread and more contagious nature of the EG.5.1 sub-variant, the reduced neutralization effects of monoclonal

antibodies and vaccines highlight the importance of discovering effective new drug candidates. This study demonstrated the potential efficacy of 3-substituted benzoxazolone Mannich bases which were considered potential new drug candidates against the emerging EG.5.1 variant. The molecular docking study provides preliminary data for future *in vitro* and *in vivo* studies. *In addition*, this research might shed light on future bioinformatics-driven virology investigations that encompass both computational and laboratory-based approaches.

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Conflict of interest

There are no conflicts of interest to disclose.

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