



Computational Investigation of Selected Antivirals and mAbs Targeting the RBD of Omicron to Get Insights into Structure and Binding Attributes

Sudheer Kumar Katari^{✉,1,*} Kesavi HimaBindhu Vuyyuru^{✉,1} Anil Kumar Singh^{✉,2,*}

¹ Department of Biotechnology, Vignan's Foundation for Science, Technology and Research, Vadlamudi, Guntur 522213, India

² Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India

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Abstract

Multiple mutations in SARS-CoV-2 (nCoV) have led to the emergence of VOCs. Mutations in the receptor-RBD can significantly influence viral interaction with cell surface receptors, alter pathogenicity, and facilitate immune evasion. Such VOCs pose a significant public health risk due to their ability to evade immune responses, as well as their altered pathogenicity and transmissibility. To address these challenges, we investigated the structure, function, and binding efficiency of the RBDs of VOCs using selected antiviral drugs and mAbs. The SSEs of the S protein of VOCs were found to comprise 26.79–29.43% α -helices (Hh), 21.64–22.37% extended strands (Ee), 3.54–5.12% β -turns (Tt), and 45.40–46.84% random coils (Cc). Docking simulations revealed that the nCoV-RBD-lopinavir complex exhibited the lowest binding affinity (-8.8 ± 0.55 Kcal/mol), by forming hydrogen-bond interactions with ALA-27 and ALA-143 residues. Similarly, the Omicron RBD-indinavir complex exhibited the lowest binding affinity (-7.4 ± 0.06 Kcal/mol), involving residues ARG355, ASP428, THR430, SER514, and GLU516 in hydrogen-bond interactions. Protein-protein docking of the Omicron RBD-ACE2 complex revealed a favorable docking score of -846.2 , compared with the reference complex (-703.1). The findings presented herein highlight substantial structural and functional alterations in the Omicron RBD compared with the reference nCoV RBD. This variation showcases the diverse binding affinities of selected antiviral drugs and mAbs. These findings may pave the way for experimental validation and contribute to a deeper understanding of potential therapeutic options against SARS-CoV-2 and related diseases.

Keywords:

receptor binding domain; spike protein; docking simulations; Omicron-RBD binding; variant of concern

1. Introduction

The genus Betacoronavirus includes the SARS-CoV, the MERS-CoV, and SARS-CoV-2, the causative agent of COVID-19 [1]. SARS-CoV-2 is an emerging coronavirus that originated in China in late 2019 and caused the severe illness known as COVID-19. Similar to the previously identified highly pathogenic human coronavirus SARS-CoV, the causative agent of SARS, SARS-CoV-2 is believed to have a zoonotic origin; however, the exact chain of animal-to-human transmission remains un-

clear [2]. SARS-CoV-2 possesses a positive-sense single-stranded RNA [(+) ssRNA] genome that conforms to the typical gene organization characteristic of coronaviruses, including those associated with pandemic outbreaks. It possesses one of the largest RNA genomes, approximately 30 kilobases in length, and is responsible for encoding approximately 29 proteins [3]. The genomic RNA of SARS-CoV-2 has two ORFs. These are referred to as ORF1a and ORF1b. SARS-CoV-2 contains a frameshift at the 5' end of its genome, situated at the boundary between ORF1a and ORF1b, facilitating the production of two polypep-

* Corresponding Author:

Sudheer Kumar Katari, Department of Biotechnology, Vignan's Foundation for Science, Technology and Research, Vadlamudi, Guntur 522213, India, katari319@gmail.com;
Anil Kumar Singh, Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India, phd.anil@yahoo.com



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tides that are subsequently proteolytically processed to yield 16 NSPs (Nsp1-16). The majority of SPs are encoded at the 3'-end [4]. Nonetheless, only a few vital virion proteins, such as S as SP and Mpro as NSP, have been carefully investigated as potential drug binding targets for therapeutic prospects [5–9]. WGS has demonstrated significant utility in tracking the genetic evolution of SARS-CoV-2 and detecting novel variants. WGS enables the identification of mutations across the entire viral genome, particularly in key structural proteins such as S, M, and E, which may influence viral transmission and immune evasion. Alongside WGS, methods such as Pangolin (Phylogenetic Assignment of Named Global Outbreak Lineages) are extensively used to classify SARS-CoV-2 lineages via the examination of mutation patterns in viral genomes [10,11].

GISAID and Nextstrain have enabled global data sharing and real-time tracking of variants, thereby supporting timely genomic surveillance efforts [12,13]. The S protein of the virus interacts with human host receptors, which exhibits substantial immunogenicity, and is crucial for both diagnostic and therapeutic research. Meanwhile, the RBD of the S protein facilitates viral entry into host cells primarily by interacting with the host ACE2 receptor. Furthermore, Mpro, a well-characterized SARS-CoV-2 enzyme, has been extensively studied as a potential therapeutic target for evaluating drug binding affinity, owing to the lack of close human homologs [14–22]. At eleven conserved cleavage sites, Mpro cleaves viral replicase polyproteins, thereby activating the replicase complex and facilitating the completion of the viral replication cycle. Protein functional and structural properties are critical for binding a diverse variety of pharmacologically active chemicals as ligands in the search for a viable therapeutic solution to address the associated illness. The continuous evolution of structural proteins hampers the determination of binding affinities for both novel and existing antiviral drugs targeting these proteins [22–24]. Since the onset of the COVID-19 pandemic and the continued evolution of SARS-CoV-2, the WHO has identified several VOCs and VOIs. These designations are based on their potential to spread, replace earlier variants, trigger new waves of infection, and necessitate changes in public health strategies. Continuous mutations in SARS-CoV-2 have led to the emergence of VOCs, which pose a heightened public health risk compared with earlier strains. VOCs are characterized by increased transmissibility and an enhanced ability to evade diagnostics, therapeutics, and vaccine-induced immunity [25–27].

Among the identified VOCs, Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Kappa (B.1.617.1), Delta (B.1.617.2), and Omicron (B.1.1.529) are notable variants

that have had a global public health impact [26–34]. In this regard, the BA.1 lineage has been reported to carry 60 mutations, of which up to 38 are located in the S protein, one in the E protein, two in the M protein, and six in the N protein [35]. Comparably, the BA.2 lineage has 57 mutations, 31 of which are in the S protein, and its N-terminus varies significantly from that of BA.1. lineage [35]. The RBD of S protein binds to the host ACE2 receptor, potentially enhancing infectivity and facilitating immune evasion, including reduced susceptibility to vaccine-induced neutralizing antibodies due to mutations [35]. Consequently, mutations in the RBD of the S protein have attracted considerable attention, making it a key target for extensive research. Alterations in the NTD may facilitate viral immune evasion, whereas changes in the S2 region may enhance the membrane fusion process and promote more efficient entry into host cells [36]. Mutations in the S protein of Omicron may significantly impair antibody-mediated neutralization and increase the risk of reinfection, thereby raising considerable concern [37,38]. In this perspective, mutations and structural changes in the S protein may contribute to an additional issue beyond the previous problem. Structural investigations of S proteins from VOCs, along with targeted screening of their RBDs against various antiviral drugs and mAbs, may enhance current understanding and aid in addressing the associated challenges. Drug discovery is a scientifically challenging, long-lasting, and costly process. Existing antiviral drugs may be repurposed to target the RBD of S protein and inhibit its function. The present study investigates the structural characteristics of VOCs, as well as the binding efficiency of selected drugs and mAbs to the RBDs of Omicron and nCoV. Protein–protein interactions among the RBD, ACE2, and mAbs were investigated to elucidate molecular interactions, using the WT reference variant for comparison. However, computational findings require validation through *in vitro* studies and other appropriate experimental assays to facilitate their translation into therapeutic applications.

2. Methods

2.1. Selection of Antiviral Agents Against RBD

Several antiviral agents have been repurposed for the treatment of COVID-19. In line with the published scientific literature, a set of eight antiviral drugs and two mAbs were selected for binding analysis and protein–protein interaction studies. The selected antiviral agents—remdesivir, atazanavir, indinavir, lopinavir, favipiravir, molnupiravir, oseltamivir, and ribavirin—along with two mAbs (B38

and CA521), were included in the present study [39–48]. Two-dimensional structures (2D coordinates) in SDF format (antiviral drugs) were retrieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov>), while mAb protein structures were obtained from the Protein Data Bank (PDB) (<https://www.rcsb.org>) [49–53]. Ligands

(Table 1) were prepared and adjusted to human physiological pH, followed by structure optimization and refinement for geometric accuracy using the mmff94 algorithm in Avogadro (Version 1.2.0) [54,55]. Similarly, the protein structures of the antibodies were optimized by removing other associated components.

Table 1: Molecular properties of selected antiviral drugs and monoclonal antibodies for binding analyses with the RBD of Omicron and nCoV.

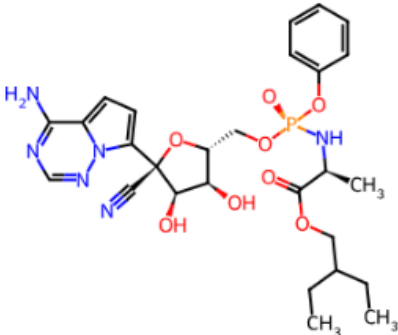
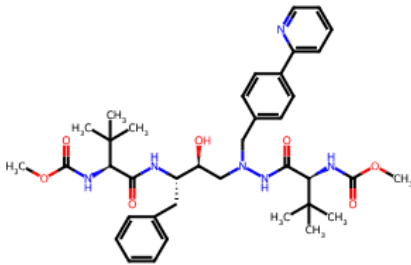
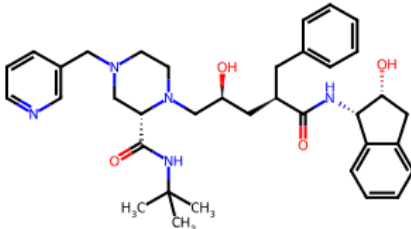
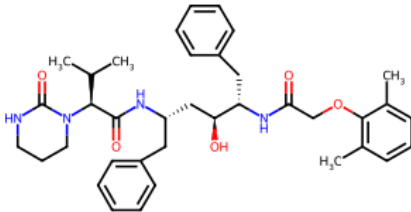
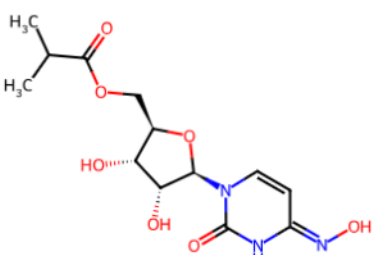
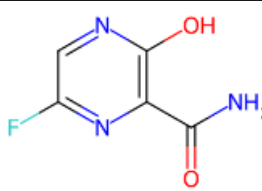
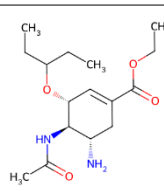
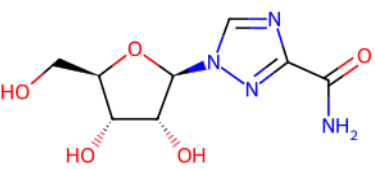
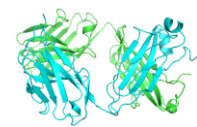
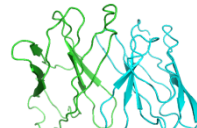
S.NO	Name	Molecular Formula	Molecular Weight (g/mol)	Structure	Type
1	Remdesivir	C ₂₇ H ₃₅ N ₆ O ₈ P	602.6		Antiviral drug
2	Atazanavir	C ₃₈ H ₅₂ N ₆ O ₇	704.9		Antiretroviral protease inhibitor
3	Indinavir	C ₃₆ H ₄₇ N ₅ O ₄	613.8		Antiretroviral protease inhibitor
4	Lopinavir	C ₃₇ H ₄₈ N ₄ O ₅	628.8		Antiretroviral protease inhibitor

Table 1: *Cont.*

S.NO	Name	Molecular Formula	Molecular Weight (g/mol)	Structure	Type
5	Molnupiravir	C ₁₃ H ₁₉ N ₃ O ₇	329.31		Antiviral prodrug
6	Favipiravir	C ₅ H ₄ FN ₃ O ₂	157.10		Antiviral drug
7	Oseltamivir	C ₁₆ H ₂₈ N ₂ O ₄	312.40		Antiviral drug
8	Ribavirin	C ₈ H ₁₂ N ₄ O ₅	244.20		Antiviral drug
9	B38	NA	NA		MAb
10	CA521	NA	NA		MAb

2.2. Extraction and Structural Preparation of RBD and ACE2

Mutations in nCoV have led to the emergence of new VOCs. A protein coordinates file (PDB) of the S protein in PDB format was deployed for structural analyses including; nCoV (PDB: 6VSB), Alpha (PDB: 7LWV), Beta (PDB: 7LYO), Gamma (PDB: 7V78), Kappa (PDB: 7V7E), Delta (PDB: 7V7Q), and Omicron (PDB: 7T9K) by retrieved from the Protein Data Bank (<https://www.rcsb.org>) [49,56–61].

Additionally, only the PDB files of the nCoV and Omicron variants were prepared for binding studies with selected antiviral drugs by trimming extraneous amino acid residues and retaining only the RBD region. This optimized portion was subsequently utilized in docking. The crystal structure of ACE2 was obtained using PDB 7C8D for the protein-protein docking [62,63]. The ACE2 region was extracted from PDB 7C8D by removing unneeded fused protein structures [62]. Moreover, the structures of all proteins were analyzed to ensure the

absence of water molecules in their coordinate files, along with the correction of missing residues.

2.3. Computational Structural Analyses

Structural analyses of S proteins of SARS-CoV-2 VOCs were conducted to understand their architecture by examining constituent amino acid residues in cartoon representation and comparing all variants. All associated PDBs of S proteins were utilized for structural overlay through the Needleman-Wunsch algorithm, employing the BLOSUM62 matrix with a cutoff distance of 2 Å [64].

2.4. Secondary Structure Prediction and Analyses

Proteins are primarily described by their SS, which include helices, turns, sheets, coils, and more, and were investigated for SARS-CoV-2 VOCs utilizing the SOPMA method (https://npsa.lyon.inserm.fr/cgi-bin/npsa_automat.pl?page=/NPSA/npsa_sopma.html). In SS prediction, the number of conformational states was set to four (helix, turn, sheet, and coil), the similarity threshold was set to 8, and the window width was set to 17. Following the input of the FASTA sequence, the data were processed using the specified configuration parameters, and the results were subsequently generated.

2.5. Structural Domain Prediction Among S Proteins of VOCs

In proteins, domains represent distinct functional and/or structural units. They are typically associated with specific functions or interactions and play a crucial role in protein activity by mediating these functions or interactions. Domains can be identified across various biological contexts, with similar domains present in proteins that serve different functions. The InterPro database from EMBL-EBI (<https://www.ebi.ac.uk/interpro/>) was used to predict structural domains in SARS-CoV-2 VOCs [65,66]. InterPro provides functional analysis of proteins by classifying them into families and predicting domains as well as key functional sites [67]. InterPro was used to identify and characterize the NTD, RBD, and S1/S2 regions across all SARS-CoV-2 variants.

2.6. Binding Affinity Assessment of Selected Drugs by Employing Docking

Docking was performed in GUI mode to dock selected drug compounds to the RBD of Omicron and the reference protein (RBD of nCoV) using the PyRx software (v. 0.8), which is coupled with AutoDock Vina. A grid box

of $44.72 \times 53.56 \times 93.25$ Å (X, Y, Z coordinates) was utilized to designate the 3D search area on the prepared proteins where the ligands are expected to bind. Vina exhibits that the highest-ranking binding free energy consistently has a 0 RMSD. The lowest-binding free-energy-ranked pose was considered, corresponding to an RMSD of 0. The resulting protein–ligand complexes were further analyzed for potential hydrogen bond interactions with key amino acid residues using UCSF ChimeraX and Discovery Studio Visualizer (v16.1.0.15350) [64,68].

2.7. Protein-Protein Docking Analyses for Exploration of RBD-ACE2, RBD-mAbs Interaction

Protein–protein docking determines the optimal orientation (binding pose) of two interacting molecules by maximizing steric and physicochemical complementarity. To conduct the protein–protein docking of Omicron-ACE 2, nCoV-ACE 2, Omicron-RBD-B38, nCoV-B38, Omicron-RBD-CA521, and nCoV-CA521, the ClusPro 2.0 server (<https://cluspro.bu.edu/publications.php>) was utilized for the analysis [69]. The server executes three computational operations in the following order: (1) rigid-body docking by sampling billions of conformations, (2) RMSD based clustering of the 1000 lowest energy structures generated to identify the largest clusters that will represent the most likely models of the complex, and (3) refinement of selected structures using energy minimization [69]. The ClusPro free docking protocol comprises two primary phases [70]. The first step is to run PIPER, a docking tool that uses the fast Fourier transform (FFT) correlation approach to seek complicated conformations on a grid [71]. Desolvation contributions are estimated using a structure-based pairwise potential in combination with van der Waals interaction energy and an electrostatic energy component. Secondly, ClusPro uses pairwise RMSD as a distance metric to cluster the top 1,000 structures generated by PIPER. The weighting coefficients of the docked protein complexes were calculated using the following equation:

$$E = 0.40E_{\text{rep}} + -0.40E_{\text{att}} + 600E_{\text{elec}} + 1.00E_{\text{DARS}}$$

3. Results

3.1. Computational Structural Analyses

Three-dimensional structures of S proteins from SARS-CoV-2 VOCs were predicted to evaluate structural similarities through residue-to-residue alignment by superimposing each S protein. PDB data for each variant,

including nCoV (6VSB), Alpha (7LWV), Beta (7LYO), Gamma (7V78), Kappa (7V7E), Delta (7V7Q), and Omicron (7T9K), were utilized for structural prediction and analysis in a single unit refined structure in cartoon without any existing ligand. **Figure 1** illustrates the structural

superimposition of the S protein of VOCs, while the RBD of Omicron and nCoV, with a distance cutoff value of 2 Å RMSD, is rendered in **Figure 2**. An overlay-generated image clearly illustrates minor color-coded variations in the protein secondary structure.

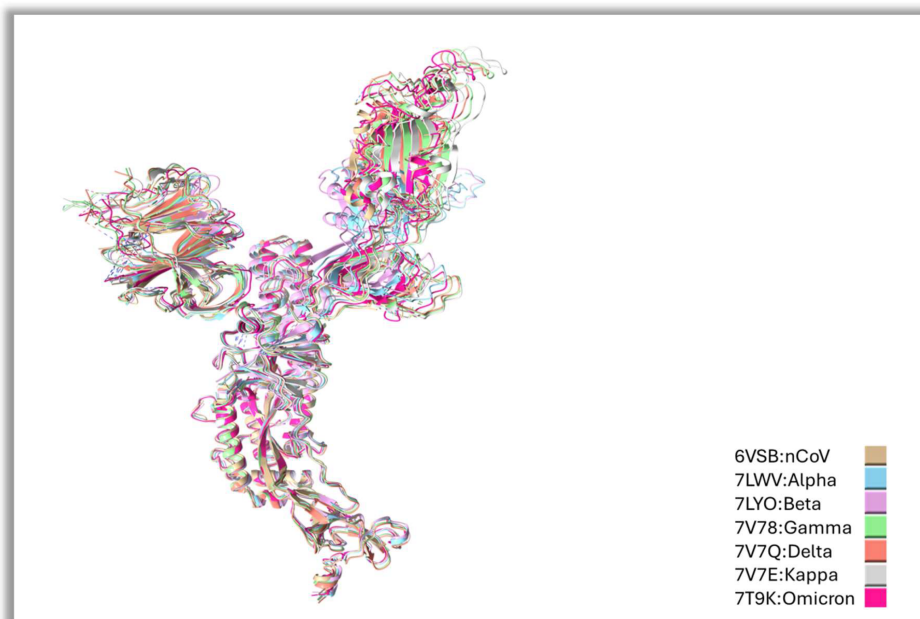


Figure 1: Structural comparison by aligning residue to residue as a superimposition of the S protein of VOCs. VOCs have been marked in the color code key as shown in the bottom right of the above figure.

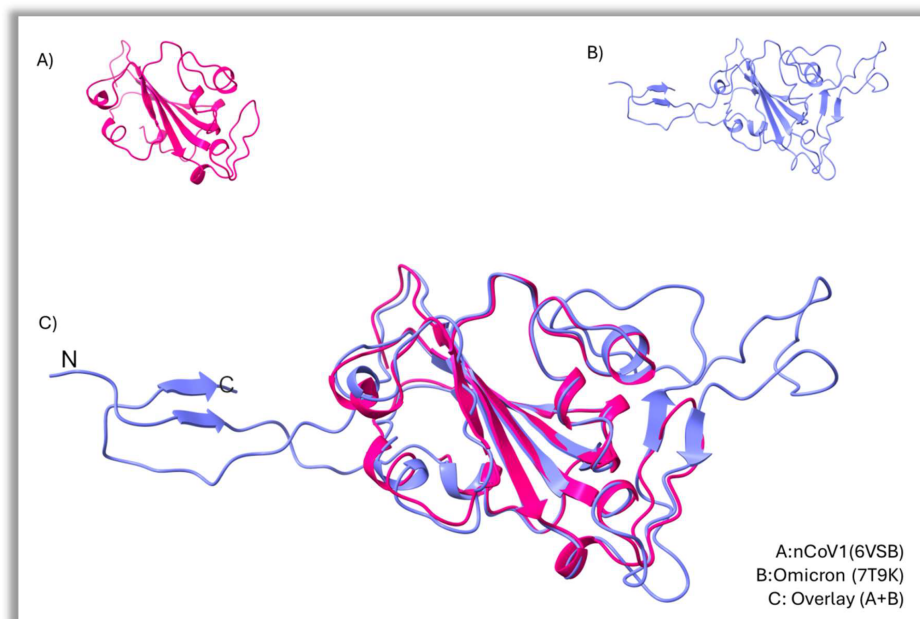


Figure 2: Structural comparison of RBD of Omicron and nCoV, with a distance cutoff value of 2 Å RMSD, in cartoon rendered. A clear change can be observed in Omicron, which has a slightly larger N-terminal and a similar C-terminal that extends to the left (**A**): nCoV1(6vsb), (**B**): Omicron (7T9K), (**C**): Overlay (A + B).

3.2. Secondary Structure Prediction and Analyses

The SSEs of VOCs, including helices, sheets, turns, and coils, were predicted using the SOPMA method. Notable variations were observed across all secondary structure profiles. The Beta (B.1.351) type possessed the lowest percentage of Alpha helix (Hh) at 26.79%, while Omicron

possessed the highest percentage at 29.43%. Extended strands were found to range from 21.64% to 22.37% across all VOCs. β -turns were observed in all VOCs within a range of 3.54% to 5.12%. Random coils were present within the range of 45% to 46.84%. **Table 2** provides a comprehensive summary of the predicted secondary structure results. A comparative SSE plot of S proteins of VOCs is shown in **Figure 3**.

Table 2: Secondary structure elements (SSE) assessment of spike protein among emerging variants of concern (VOCs) of SARS-CoV-2.

SARS-COV-2 Variant	Alpha Helix (Hh) (%)	Extended Strand (Ee) (%)	Beta Turn (Tt) (%)	Random Coil (Cc) (%)
nCoV	26.86	21.97	5.12	46.04
Alpha (B.1.1.7)	27.70	21.71	4.44	46.15
Beta (B.1.351)	26.79	21.97	4.66	46.58
Gamma (P.1)	27.12	22.37	4.52	45.99
Kappa (B.1.617.1)	27.67	22.06	3.82	46.45
Delta (B.1.617.2)	27.09	21.86	4.22	46.84
Omicron (B.1.1.529)	29.43	21.64	3.54	45.40

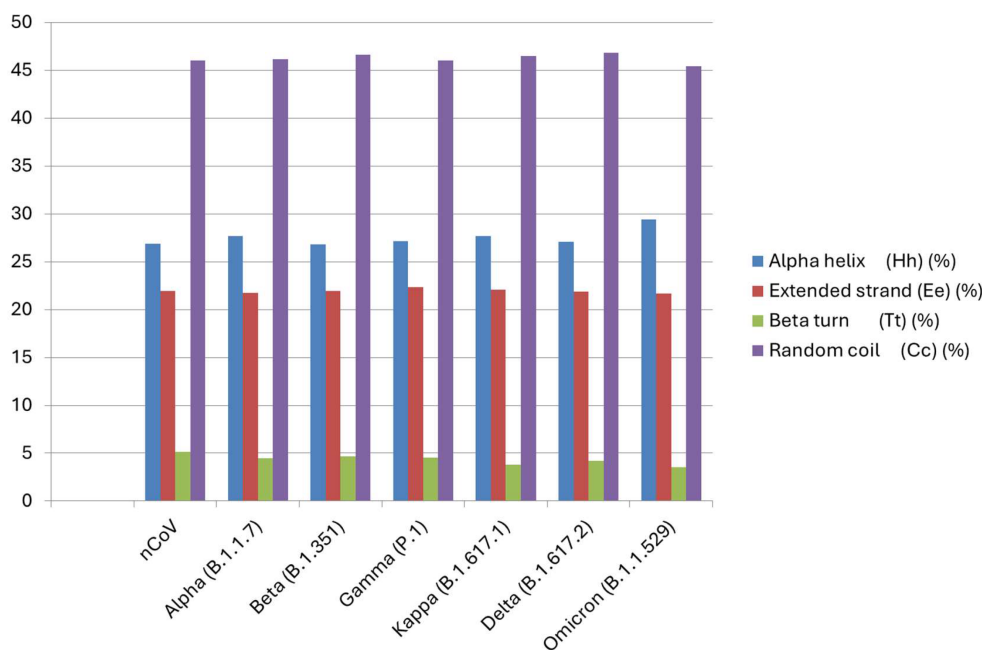


Figure 3: Comparative SSE plot of S proteins from VOCs is shown as percentages of elements.

3.3. Structural Domain Prediction Among S Proteins of VOCs

Identifying and predicting specific protein structural regions is a crucial aspect of understanding protein structure and function. Protein motifs and domains represent

unique, functional evolutionary units that can be acquired, lost, or rearranged collectively as a single module more readily than other protein elements. This evolutionary flexibility enables the rapid assembly of proteins by combining existing functional modules, thereby contributing

to protein diversity and the emergence of novel functions. InterPro performs functional analysis of proteins by classifying them into families and predicting domains and key functional sites based on a given protein sequence. Structural domains from all S proteins of VOCs were predicted

to encompass the variable region of amino acid residues. The predicted domain in the S protein among all VOCs is listed in **Table 3**. Residue-to-residue structural comparison of the Omicron and nCoV S proteins is shown in **Figure 4**.

Table 3: Amino acid sequence details in the structural domain of the spike protein in different variants of concern (VOCs).

S.NO	Spike Protein of SARS-CoV-2	PDB ID	Structural Domain	Amino Acid Range
1	nCoV	6VSB	NTD	13–304
			S1-RBD	319–541
			S1/S2	543–1208
2	Omicron	7T9K	NTD	13–301
			S1-RBD	330–513
			S1/S2	540–1205

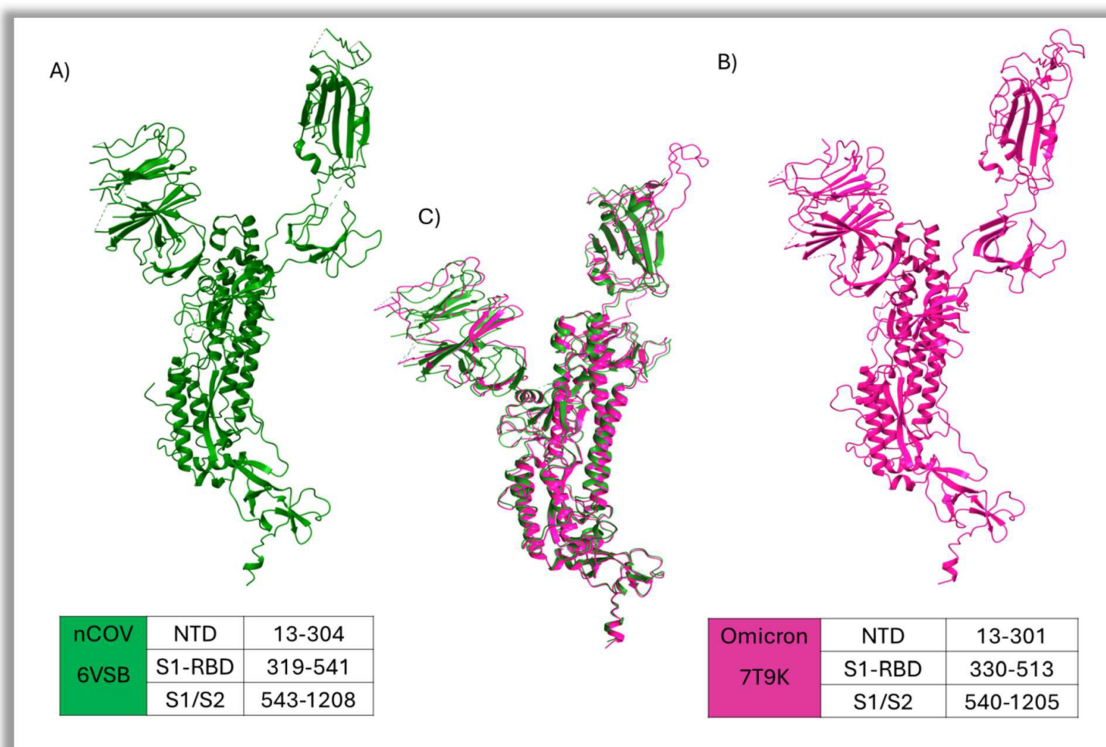


Figure 4: Structural depiction of spike protein with its structural domain details, and structural comparison. (A) Represents the spike protein of nCoV (6VSB). (B) represents spike protein of Omicron (7T9K). (C) overlay of both structures within 2Å RMSD. The structural domain comprising NTD, S1-RBD, and the S1/S2 region is described in the corresponding table at the bottom.

3.4. Binding Affinity Assessment of Selected Drugs by Employing Docking

Molecular docking is a reliable computational method for investigating receptor–ligand interactions. This step is

crucial for pre-screening or virtual screening in the drug discovery and development process, as well as in repurposing efforts. Hydrogen bonding and active-site residues, along with the lowest binding energy and lowest RMSD, are essential parameters for evaluating docking perfor-

mance in drug–ligand interaction studies. A collection of eight drug candidates was docked with RBD (Omicron), and the results were compared to the nCoV (wild type) variant to evaluate the binding ability with corresponding ligands (Drugs). The RBD-Indinavir complex of Omicron (7T9K) exhibited the lowest binding with a binding affinity value of -7.4 ± 0.06 (Kcal/mol), involving H-Bond interactions with ARG-355, ASP-428, THR-430, SER-514, and GLU-516 residues. Similarly, the RBD–lopinavir complex of nCoV (6VSB) exhibited a binding affinity of -8.8 ± 0.55 Kcal/mol, indicating the lowest binding affinity, which is comparatively stronger than Omicron’s top-ranked molecule and involves hydrogen bonding with ALA27 and ALA143 residues. RBD of nCoV exhibited good binding affinity in a range of -5.7

± 0.64 to -8.8 ± 0.55 Kcal/mol, in contrast to Omicron, which showed binding affinity in a range of -5.2 ± 0.26 to -7.4 ± 0.06 Kcal/mol. Residues PRO-330, ASN-331, THR-333, ASN-334, GLU-340, ARG-346, ASN-354, ARG-355, ASN-360, VAL-362, SER-99, ASP-428, THR-430, ARG-454, ARG-457, SER-459, GLU-471, SER-494, SER-496, ARG-498, TYR-501, SER-514, GLU-516, LEU-517, CYS-525, and LYS-528 were found to be involved as common active-site amino acids involved in hydrogen-bond interactions. Figures 5 and 6 depict the two-dimensional protein–ligand interactions of the Omicron and nCoV RBDs. Table 4 presents the docking assessment results in comprehensive detail. Figure 7 depicts a comparison binding affinity plot of Omicron–ligands and nCoV–ligands.

Table 4: Binding affinity assessment of antiviral drugs and RBD (nCoV and Omicron) to understand the molecular interactions.

RBD-Docked Complex		Binding Affinity (Kcal/mol) (Mean $\pm$ SD, n = 3)	Interactive Amino Acid Residues	Chemical Bonding
Omicron (7T9K)	Remdesivir	-6.2 ± 0.19	SER-494, SER-496, ARG-498, TYR-501	H-bond
	Atazanavir	-6.6 ± 0.28	LEU-517	H-bond
	Indinavir	-7.4 ± 0.06	ARG-355, ASP-428, THR-430, SER-514, GLU-516	H-bond
	Lopinavir	-5.2 ± 0.26	ASN-360, CYS-525	H-bond
	Molnupiravir	-5.8 ± 0.31	ARG-454, ARG-457, SER-459, GLU-471	H-bond
	Favipiravir	-5.9 ± 0.61	GLU-340, ARG-346, ASN-354, SER-399	H-bond
	Oseltamivir	-5.3 ± 0.79	ASN-331, ASN-334, VAL-362	H-bond
	Ribavirin	-5.9 ± 0.26	PRO-330, THR-333, VAL-362, LYS-528	H-bond
nCoV (6VSB)	Remdesivir	-7.4 ± 0.43	PHE-6, SER-37	H-bond
	Atazanavir	-8.1 ± 0.22	ASN-7, SER-35	H-bond
	Indinavir	-8.0 ± 0.11	ALA-36	H-bond
	Lopinavir	-8.8 ± 0.55	ALA-27, ALA-143	H-bond
	Molnupiravir	-6.7 ± 0.78	PHE-6, ASN-7, VAL-31	H-bond
	Favipiravir	-5.7 ± 0.64	ALA-27, TYR-29, LEU-54, PHE-56, THR-144	H-bond
	Oseltamivir	-6.6 ± 0.37	PHE-2, GLY-3, ASP-28	H-bond
	Ribavirin	-6.3 ± 0.87	ASP-62, TYR-87, ASP-92, THR-94, SER-135	H-bond

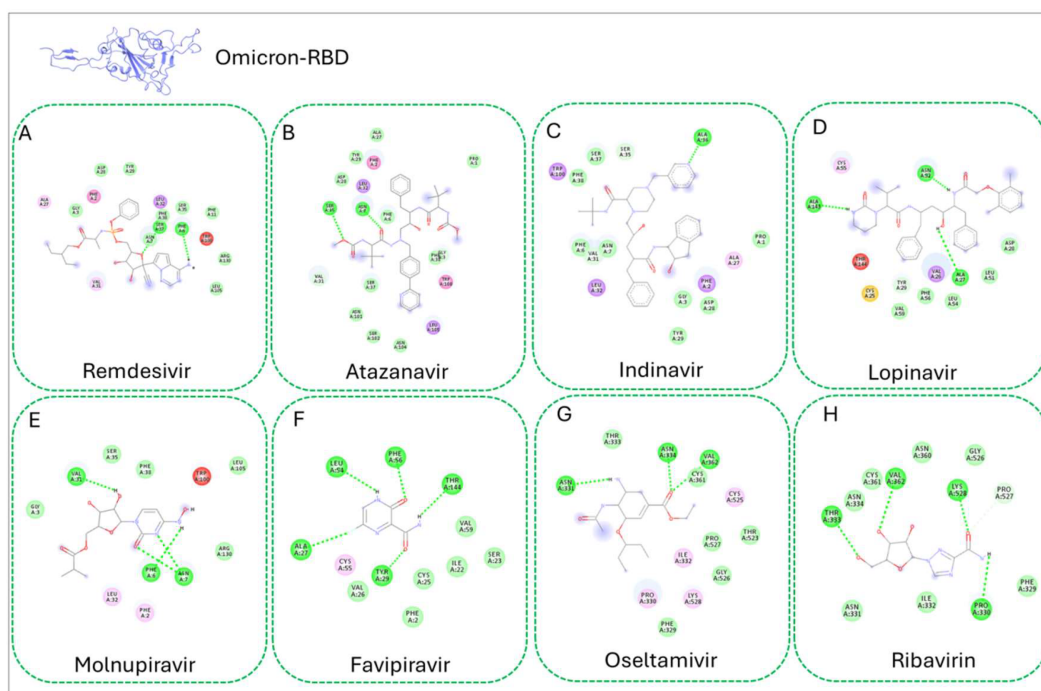


Figure 5: Docking pose of the protein-ligand interaction of Omicron with selected drugs (A) Remdesivir, (B) Atazanavir, (C) Indinavir, (D) Lopinavir, (E) Molnupiravir, (F) Favipiravir, (G) Oseltamivir, (H) Ribavirin. H-bonds among the corresponding ligands are shown in the 2D interaction figures.

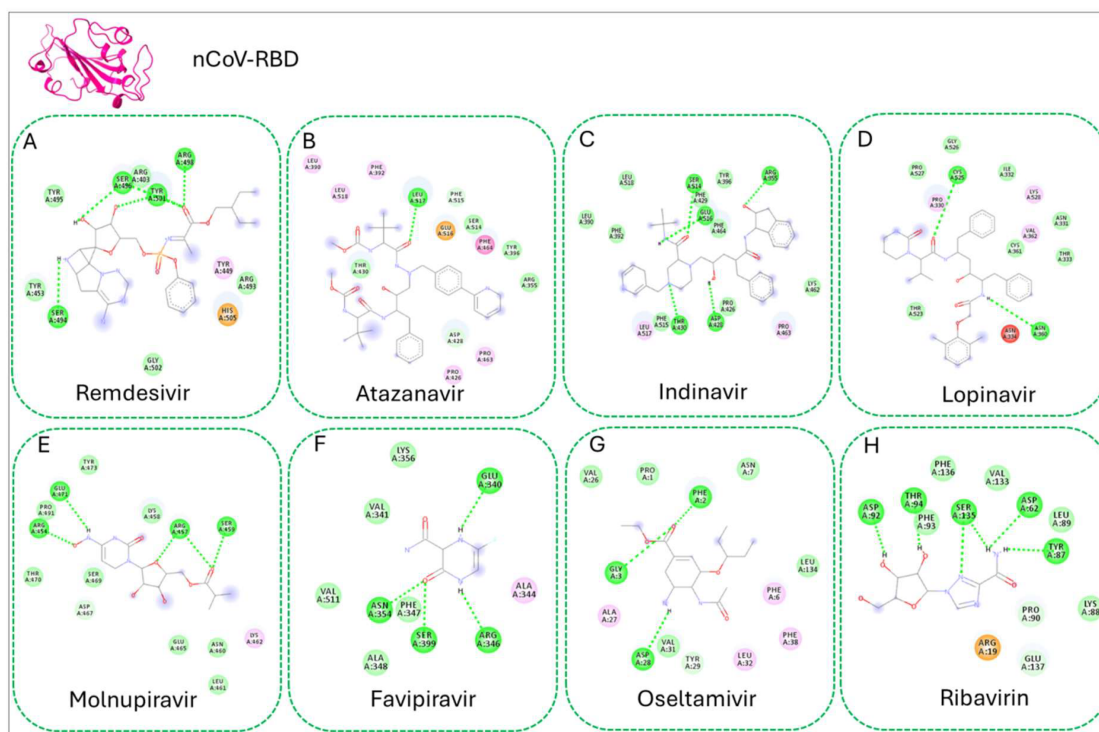


Figure 6: Docking pose of the protein-ligand interaction of nCoV with selected drugs (A) Remdesivir, (B) Atazanavir, (C) Indinavir, (D) Lopinavir, (E) Molnupiravir, (F) Favipiravir, (G) Oseltamivir, (H) Ribavirin. H-bonds among the corresponding ligands are shown in the 2D interaction figures.

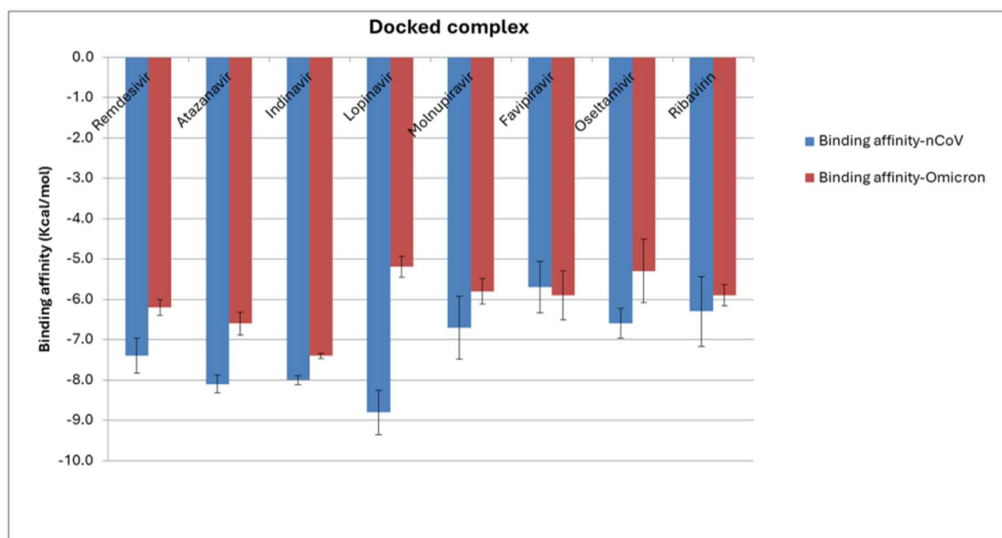


Figure 7: Highlights a comparative binding affinity plot of Omicron-ligands and nCoV-ligands docked complexes.

3.5. Protein-Protein Docking Analyses for Exploration of RBD-ACE2, RBD-mAbs Interaction

Protein-protein docking is crucial for examining protein-protein interactions and emphasizing interactional functionalities. The Omicron RBD-ACE2, Omicron RBD-B38, and Omicron RBD-CA521 complexes were docked to elucidate the underlying binding interactions and associated energy scores. Protein-protein docking was compared with the nCoV variant as a reference to investigate detailed interaction characteristics and to better understand Omicron binding with antibodies and the ACE2 receptor. The Omicron-ACE2 docked complex demonstrated a score of -846.2 (center) and -846.2 (Lowest Energy) for the 0 cluster, which is significantly better than the reference docked complex (nCoV-ACE2), which had a score of -648.6 (center) and -703.1 (Lowest Energy). Omicron- B38 (Antibody) protein-protein dock-

ing scores exhibited -728.0 (Center), -873.7 (Lowest Energy) scores for 0 clusters. The score values of this protein-protein complex were not substantially different from, or showed only minor fluctuations compared with, the reference docked complex (nCoV-B38), which exhibited scores of -706.8 (center) and -924.0 (lowest energy), respectively. The Omicron-CA521 (antibody) docked complex exhibited score values of -836.6 (center) and -930.7 (lowest energy), respectively, for 0 clusters. Comparatively, these scores were higher than those of the reference docked complex (nCoV-CA521), which exhibited scores of -139.4 (center) and -162.6 (lowest energy), respectively. Selected docked protein-protein complexes are highlighted in Figures 8 and 9. The protein-mAb (Omicron-antibody) and protein-ACE2 interaction results indicated significantly improved binding behavior compared with the reference complexes. Table 5 presents the comprehensive protein-protein docking results.

Table 5: Protein-protein docking scores of RBD and other proteins.

Protein-Protein Complex	Docking Score	
	Center	Lowest Energy
* nCoV-RBD-ACE2	-648.6	-703.1
Omicron-RBD-ACE2	-846.2	-846.2
* nCoV-RBD-B38	-706.8	-924.0
Omicron-RBD-B38	-728.0	-873.7
* nCoV-RBD-CA521	-139.4	-162.6
Omicron-RBD-CA521	-836.6	-930.7

* Complexes were utilized as a reference.

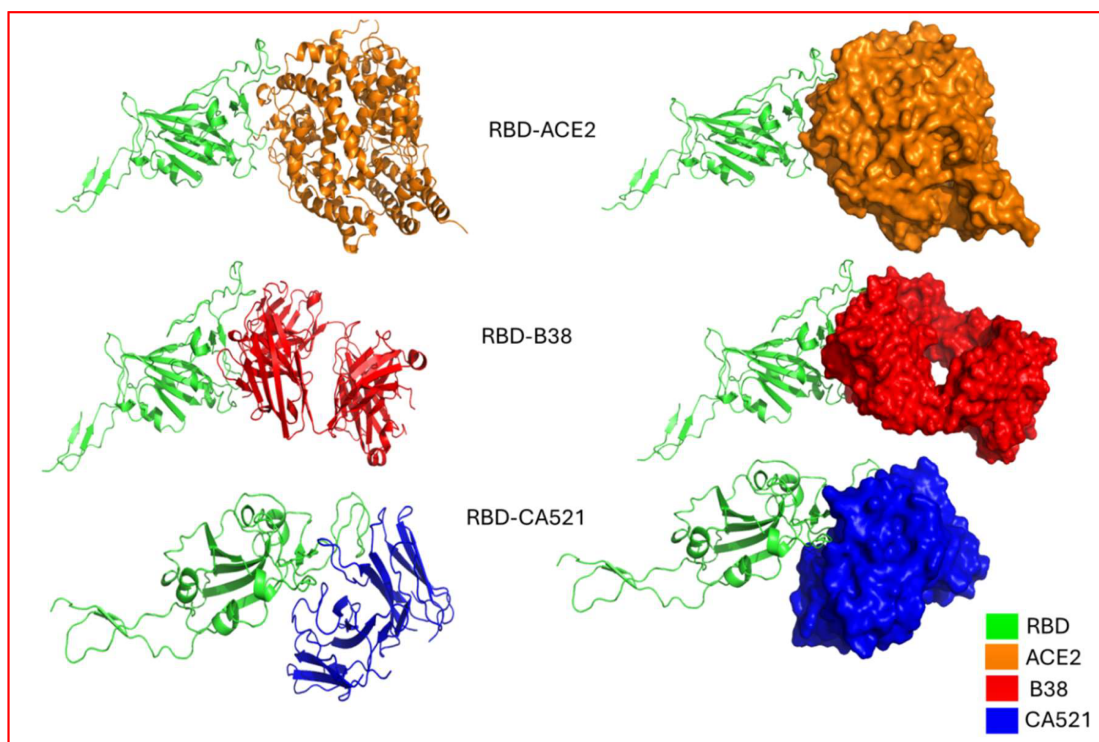


Figure 8: Protein-protein docked complexes of Omicron, with corresponding antibodies and ACE2 receptor. Color-coded keys depict the different components of docked complexes. Green: RBD; Orange: ACE2; Red: B38 antibody; Blue: CA521 antibody.

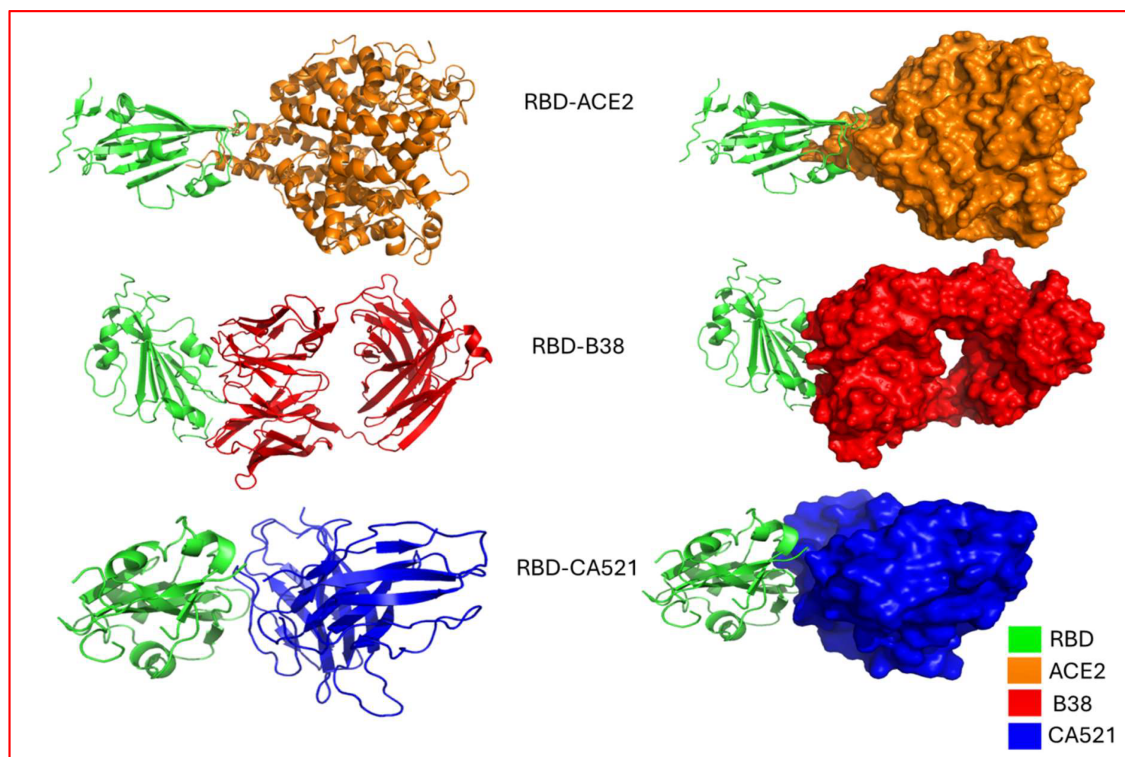


Figure 9: Protein-protein docked complexes of nCoV, with corresponding antibodies and ACE2 receptor. Color-coded keys depict the different components of docked complexes. Green: RBD; Orange: ACE2; Red: B38 antibody; Blue: CA521 antibody.

4. Discussion

SARS-CoV-2, the causative agent of COVID-19, is prone to mutations, leading to the emergence of genetic variants classified as VOCs. Since its initial emergence in 2019, SARS-CoV-2 has undergone continuous evolution, resulting in the emergence of multiple lineages and VOCs characterized by enhanced transmissibility, increased disease severity, and improved immune evasion capabilities. The WHO has designated these variants using nomenclature derived from the Greek Alphabet, starting with the Alpha (B.1.1.7) variant, which surfaced in 2020, succeeded by the Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) variants [72]. Each VOC has unique mutations in the S protein, which influence pathogenicity, transmissibility, and evasion of diagnostic tests and vaccination [73,74]. Among the various VOCs, the Omicron variant is the most genetically diverse, having evolved into multiple distinct sub-lineages that the WHO has classified as VOIs. These include BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.13, BA.2.38, BA.2.75, BA.3, BA.4, and BA.5 [72]. BA.4 and BA.5 continue to be among the most prevalent and notable variants, while several novel sub-variants—such as BA.2.75.2 (BF.7), BA.4.6, BA.4.7, BA.5.9, BF.7, BQ.1, BQ.1.1, BN.1, XBB, XBB.1.5, XBB.1.6, and CH.1.1—have emerged globally from previously circulating Omicron sub-lineages [72]. Nevertheless, a variety of medicines, including antiviral agents and a few additional antibiotics, have shown efficacy in treating novel SARS-CoV-2-associated diseases (COVID-19) [75,76]. Consequently, the most recent variant, Omicron, characterized by a notably high mutation rate, has resulted in a new phase in the global epidemic. Exploring the pathogenicity of novel SARS-CoV-2 variants could significantly enhance our understanding through integrated structural and functional studies.

Additionally, identifying the molecular interactions between antiviral drugs and antibodies will be crucial for addressing future outbreaks and treating diseases associated with SARS-CoV-2. In this instance, multiple monoclonal antibodies have also demonstrated effectiveness for both prevention and treatment of SARS-CoV-2 infection [77–79]. Further exploration remains challenging; therefore, this study investigates the structural and functional properties of S protein variations in Omicron in relation to the binding affinity of antiviral drugs and mAbs. A comprehensive evaluation was conducted on eight approved antiviral drugs to assess their binding affinity toward the RBD of the S protein of Omicron variants, with a comparative analysis against the nCoV variant to facilitate an in-depth understanding of binding behavior. Additionally, two antibodies were evaluated for their binding

interactions with the RBD, highlighting the significance of the protein-protein interaction. The structure of the entire S protein of VOCs, along with the RBD of Omicron and nCoV, reveals significant differences when analyzed through structural overlay. The constituent SSE in S proteins of VOCs ranged from 3.54% to 46.84% across all categories, including Alpha helix, Extended strand, Beta turn, and Random coil. The far lowest Alpha helix percentage was observed for nCoV as 26.86%, while the highest was noted in Omicron at 29.43%. The extended strand (Ee) content ranged from 21.64% (Omicron) to 22.37% (Gamma). β -turn (Tt) elements were the least abundant secondary structure component, ranging from 3.54% (Omicron) to 5.12% (nCoV). Random coil (Cc) element noted the highest SSE as 45.40% (Omicron) to 45.99% (Gamma). The binding affinity of the RBD with selected antiviral drugs indicates potential interactions, including hydrogen bonding with associated active-site residues.

Notable binding affinity observed for the RBD–Lopinavir complex of nCoV, with a lowest binding energy of -8.8 ± 0.55 Kcal/mol, involving the residues ALA-27 and ALA-143, which were involved in H-Bond. Similarly, the Omicron RBD–indinavir complex exhibited strong binding affinity, with a value of -7.4 ± 0.06 Kcal/mol. This exhibits hydrogen-bond interactions with ARG-355, ASP-428, THR-430, SER-514, and GLU-516 residues. The binding scores for the Omicron–ACE2 and Omicron–antibody (two mAbs) complexes indicate favorable binding energies and stable interactions. The Omicron RBD–ACE2 complex exhibited scores of -846.2 for the Center and -846.2 for the lowest energy, respectively. In contrast to the reference complex (nCoV RBD–ACE2), which exhibited a slightly lower score for center only as -648.6 , whilst the Lowest Energy score was higher (-703.1). Omicron–RBD–B38 complex was found to have a good energy Score (Center -728.0), and a weak Lowest energy score (-873.7) than the reference complex (nCoV RBD–B38), which had -706.8 (Center), and -924.0 (Lowest Energy). The Omicron RBD–CA521 complex exhibited protein–protein docking scores of -836.6 (center) and -930.7 (lowest energy) for 0 clusters. In contrast to the nCoV RBD–CA521 complex, this represents a more favorable energy profile. Overall, the protein–protein docking scores support the strong binding affinity of the Omicron RBD toward the ACE2 receptor and selected antibodies. Top-ranked docked complexes can be further validated through MDS and subsequently confirmed using *in vitro* experiments, which may enhance the understanding of Omicron functionality at the molecular level. Nevertheless, additional experimental validation can be conducted to repurpose evaluated antiviral drugs for the effective management of future SARS-CoV-2-related illnesses.

5. Conclusions

The S protein mutation results in structural changes that enhance pathogenicity, increase transmissibility, and enable immune evasion in the SARS-CoV-2 variants. The mutation appeared as the key factor in the development of a highly transmissible variant of SARS-CoV-2, which was known as Omicron. A notable mutation in the RBD of Omicron has altered its binding affinity for antiviral drugs and antibodies. Such attributes were undertaken with the present study, implementing eight antiviral drugs and two mAbs. Findings on multivalent computational parameters suggested significant changes in S proteins, including RBD, and variable binding affinity among ligands and mAb. SSE exhibited a significant variation in constituent elements among VOCs. The binding affinity of RBD (Omicron) with antiviral drugs exhibited a notable binding potential in a range of -5.2 ± 0.26 to -7.4 ± 0.06 Kcal/mol. Likewise, Protein-Protein docking further elucidated the binding dynamics between the Omicron-ACE2 receptor and selected mAb. The computational findings of selected drugs and mAb exhibited a significant binding capacity, which could be further extended by implementing MDS and experimental validation, which might be helpful for further investigation to understand the efficacy of antiviral drugs against the RBD of mutant and future sub-variants.

List of Abbreviations

ACE2	Angiotensin Converting Enzyme 2
COVID-19	Coronavirus Disease 2019
E	Envelope
FFT	Fast Fourier Transform
M	Membrane
mABs	Monoclonal antibodies
MDS	Molecular dynamics simulation
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
Mpro	Main Protease
N	Nucleocapsid protein
NSP	Non-Structural Protein
NTD	N-terminal Domain
ORFs	Open Reading Frames
RBD	Receptor-Binding Domain
RMSD	Root-Mean-Square Deviation
S	Spike Protein
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SP	Structural Protein
SS	Secondary structure
SSE	Secondary Structural Element

VOC	Variant of Concern
VOIs	Variants of Interest
WGS	Whole genome sequencing
WHO	World Health Organization
WT	Wildtype

Author Contributions

S.K.K.: Data curation, Formal analysis, Investigation, Methodology, Validation, Software, Writing—original draft, Writing—review & editing, and Supervision. K.H.V.: Data curation, Formal analysis, Investigation, Methodology, Validation, Software, Writing—review & editing. A.K.S.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Software, Project administration, Writing—original draft, Writing—review & editing, Visualization, and Supervision. All authors have reviewed and agreed to the final version of the manuscript.

Availability of Data and Materials

All data used in the present study were generated from computational experiments and are provided herein. Data associated with the results are available upon request from the corresponding authors.

Consent for Publication

No consent for publication is required, as the manuscript does not involve any copyright materials or other materials that would necessitate consent. All authors have read and approved the published version of the manuscript.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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AI Declaration

The authors confirm that no AI tools were used to generate any content of this manuscript.

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