

RESEARCH ARTICLE

Exploring Remdesivir–nsp7/nsp8 Interactions in SARS–CoV–2 Using Computational Modelling

Gargi Tiwari¹, Shiv Kumar², Madan Singh Chauhan² and Dipendra Sharma^{2*}

ABSTRACT: Remdesivir is a medicine used to treat COVID-19, or coronavirus illness, which is an infection caused by the SARS-CoV-2 virus. Remdesivir belongs to a class of antiviral drugs that inhibit viral replication within the body. This study describes the electronic properties of remdesivir, its molecular docking, and an investigation of the molecular dynamics simulation using a protein receptor. In this study, the geometry of the remdesivir molecule has been optimized using DFT at the B3LYP and ω B97XD levels with the 6-311+G(d,p) basis set in both gas and aqueous phases. A range of favorable binding sites between the residue positions of the ligand and target protein were produced by the molecular docking that was used to investigate the binding affinity of the remdesivir drug with SARS-CoV-2 nsp7+8C protein complex. The results have been reviewed to provide insight into the efficacy of the remdesivir medicine against the SARS-CoV-2 nsp7+8C complex.

Keywords: SARS-Cov-2; Nsp7+8C; Remdesivir; Docking; MD Simulation.

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1. INTRODUCTION

A novel coronavirus, also known as severe acute respiratory syndrome coronavirus-2 or SARS-CoV-2 in short was first identified in Wuhan, Hubei province, China in December 2019, resulting in the coronavirus illness 2019 (COVID-19). A nearby wet market was identified as a possible source and geographically associated with affected individuals. There are currently no published statistics on nosocomial or person-to-person transmission [1]. The 28-day period from November 11 to December 8, 2024, saw 31 nations record COVID-19 fatalities and 81 countries report COVID-19 cases worldwide. Health systems continue to face a significant cost from post-COVID-19 conditions (PCC). Although it is challenging to investigate the exact incidence of PCC, studies indicate that PCC symptoms occurred in around 6% of symptomatic SARS-CoV-2 infections [2]. Physicians throughout the world are perplexed by the SARS-

CoV-2 infection's quickly changing nature. Managing this lethal virus is made more difficult by the heterogeneity of clinical symptoms as well as the severity of the illness [3]. Olfactory dysfunction (dysosmia, hyposmia, and anosmia) and taste or gustatory disorders (dysgeusia, hypogeusia, and ageusia) are examples of atypical appearances that were once dismissed but are now considered essential. In addition to fever, cough, chills, shortness of breath, sore throat, and, muscular soreness the Centers for Disease Control has added the new onset of loss of taste and smell to its list of symptoms that may indicate a SARS-CoV-2 infection [4]. It is interesting to note that very few cases of gustatory and olfactory impairment have been documented among Asian populations, especially in China. In contrast to a multi-center European-researched that found 85.6% of COVID-19 patients had olfactory dysfunction and 88.0% of patients had gustatory dysfunction, a previous report found hypogeusia in 5.6% of cases and hyposmia in 5.1% of cases [5]. According to research, the mutation in the virus's genome is responsible for the difference in clinical presentation across various people around the globe [6]. As everyone is aware, coronaviruses are single-stranded RNA viruses that are renowned for their rapid recombination and mutation [1, 7]. The behaviour and prospective capabilities of this unique virus will be better understood with the help of in-depth

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molecular epidemiology research and analysis [3].

Numerous COVID-19 vaccines and innovative treatments (which were reused in part) were developed and approved quickly due to the pressing need to contain the pandemic and lessen the strain on healthcare systems as well as a continuing improvement in our understanding of the disease's etiology [8]. The Covid-19 vaccination pipeline produced a groundbreaking result that the entire world witnessed. Since the first line of defense against COVID-19 is vaccination, several of them have been authorized and are now undergoing various stages of clinical studies [9, 10]. Additionally, antivirals are required for medicinal purposes. On the other hand, antiviral medications for SARS-CoV-2 use a variety of tactics to prevent viral replication. For instance, inhibitor candidates that target viral attachment to host cells target the human angiotensin-converting enzyme 2 (ACE2) receptor contact and the SARS-CoV-2 spike proteins that mediate viral entrance [11–13]. Inhibiting viral proteases, major protease (M^{pro}), papain-like protease (Pl^{pro}), or 3-like proteases ($3CL^{pro}$) is another tactic [14, 15]. Additionally, in anti-SARS-CoV-2 medication design, RNA-dependent RNA polymerase (RdRp) also became a target [16]. Only a few number of drugs are now available to either prevent or treat SARS-CoV-2, including cilgavimab/tixagevimab, bebtelovimab, sotrovimab, molnupiravir, nirmatrelvir/ritonavir, and remdesivir.

Numerous research, including as PINETREE, ACTT-1, and real-world efficacy trials, have emphasized the significance of early antiviral therapy for COVID-19 [17–21]. Viral replication appears to be the primary driver of the early clinical course and immunological response to COVID-19, peaking at or just before symptom onset [22]. Instead of immunomodulatory treatment, early antiviral medication may be crucial in preventing later systemic harm brought on by a dysregulated immune response [23]. NIH and IDSA clinical guidelines support these findings by stating that remdesivir is most effective when taken initially in the treatment of COVID-19, that is, within 7 to 10 days after the beginning of symptoms [24]. Nevertheless, patients may not always be able to pinpoint the precise moment when their symptoms began, particularly when they are vague or gradual, and the therapeutic efficacy does not progressively diminish beyond this recommended treatment window [25]. Research indicates that in the majority of hospitalized patients, a shorter duration of remdesivir is necessary. In an open-label, randomized, phase 3 study, individuals having age more than 12 years who were hospitalized with severe COVID-19 and did not require mechanical breathing at baseline were treated with remdesivir for 5 and 10 days [26]. A meta-analysis and comprehensive review of eight randomized trials (including 10,751 patients) revealed a strong likelihood that remdesivir lowers mortality in COVID-19 nonventilated patients who need additional oxygen treatment [27]. In light of these considerations, the present study explores the reactivity, toxicity, and potential active sites of the remdesivir molecule using DFT approach. In order to check the inhibitory activity of the drug molecule against SARS-CoV-2 nsp7+8C protein complex [28], molecular docking

simulation has been performed. Last but not least, molecular dynamics (MD) simulations have been used to assess the drug's capacity to attach to the protein steadily.

2. COMPUTATIONAL DETAILS

2.1 DFT and Hirshfeld surface analysis

The DFT investigation has been used to optimize the geometry of the remdesivir molecule using the 6-311+G(d,p) basis set and B3LYP and ω B97XD functionals [29–38]. The electro-optical along with electronic characteristics of the drug molecule, such as its MEP surface and its HOMO and LUMO, have been computed after the optimization process. These HOMO and LUMO values have further been used for the calculation of global reactivity parameters. The literature contains the mathematical information needed to calculate electro-optical and global parameters [39, 40]. Further, the TD-DFT approach has been used to study the absorption spectra of drug molecule in gas and water mediums utilizing B3LYP functional at the same level of basis set. In the DFT study, Gaussian16W program has been used for all calculations, and GaussView6.0 has been used for visualization of DFT results [41, 42].

The method known as Hirshfeld surface analysis is used to compute and show the interactions between molecules in a chemical system. The software CrystalExplorer17.5 has been used to create two-dimensional fingerprint plots and Hirshfeld surface analysis [43].

2.2 The molecular docking and molecular dynamics simulations

A molecular modelling method called docking is used to forecast the interactions between remdesivir molecule and SARS-CoV-2 nsp7+8C protein receptor. For this, SwissDock web server [44] has been utilized and the docking outcomes have been visualized on Chimera software [45]. The best docked posture has further been used for MD simulation study. Using MD simulation, the stability of the suggested active site of ligand binding to the protein receptor has been studied, and the inhibitor-receptor interaction has been thoroughly probed. This has been accomplished by running the MD simulation with CHARMM General Force Field (CGenFF) for 100 ns using the NAMD software program [46, 47]. The NAMD data has been visualized using the VMD software [48]. In this study, we calculate the binding free energy using the MM/GBSA computation on a solvated complex using the multi-MD trajectory technique. The chosen docked positions have been scored using the Molecular Mechanics Generalized Born Solvation Area (MM/GBSA) model in order to examine the biological activities that have been observed. Various steps employed in MD simulations for trajectories analysis are depicted in Figure 1.

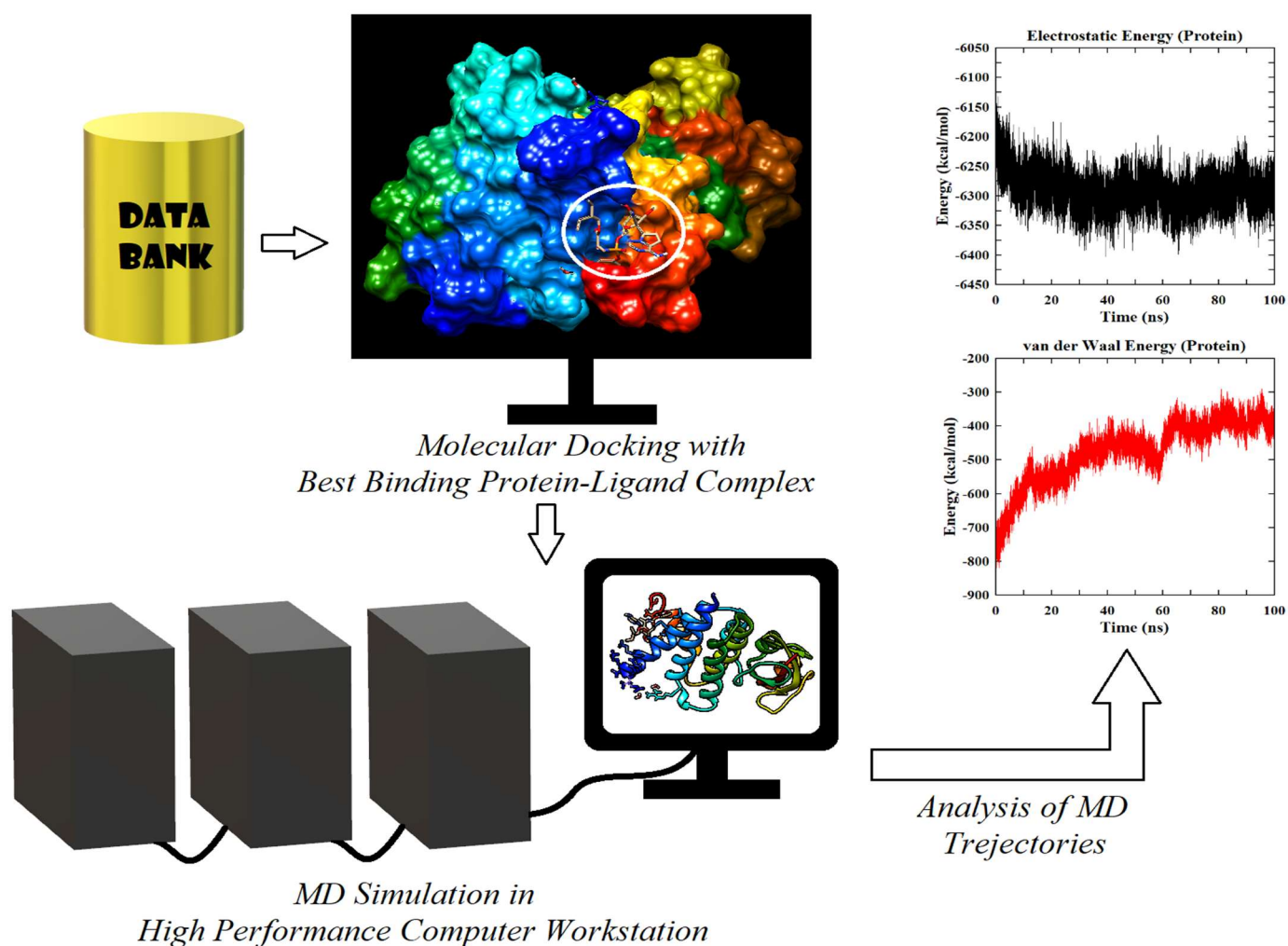


Fig. 1. Various in silico processes for MD simulation trajectories analysis.

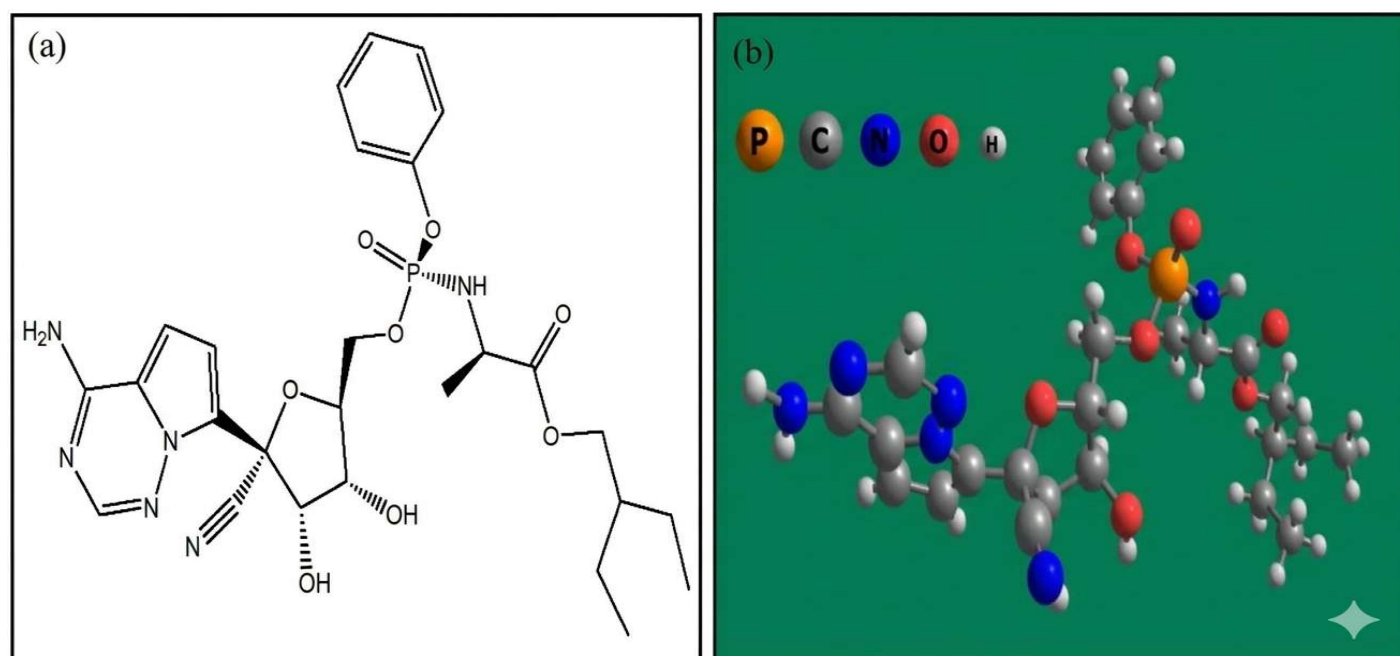


Fig. 2. Remdesivir drug (a) chemical structure and (b) optimized geometry by B3LYP method.

3. RESULTS AND DISCUSSION

3.1. DFT investigation of electronic, global reactivity descriptor, NLO parameters and UV-vis spectra of remdesivir

The chemical structure of remdesivir molecule is depicted in Figure 2(a). The optimized geometry of remdesivir molecule as obtained by running the Gaussian 16W program in conjunction with the DFT/B3LYP technique using 6-311+G(d,p) basis set in gas and aqueous medium is provided in Figure 2(b). Same procedure has been repeated for DFT/ ω B97XD method in order to check the minimum ground state energy of the drug molecule in both mediums. It is evident from Table 1, the minimum electronic energy of remdesivir molecule computed by both techniques and in two mediums are approximately same. Further, the two equilibrium geometries have been used to investigate the electronic and global parameters along with electro-optical and NLO parameters of the compound. The geometry of the molecular orbitals of organic compounds, in addition to the orbitals' nature, directly correlates with their chemical and biological activity [49]. Frontier molecular orbitals (FMO) are decisive in the study of drugs because they help to recognize the type and efficient way that ligands interact with neighbouring protein receptors. Therefore, it is important to analyse HOMO-LUMO maps in order to get accurate qualitative data on the drug's vulnerability to interacting with biological organisms. Calculating molecular reactivity characteristics like ionization potential, electron affinity, electronegativity, electrophilicity index, hardness, and softness also requires the use of FMO data in terms of HOMO and LUMO values [50].

Charge transport through the molecule has been shown by the calculation of HOMO and LUMO energies, which is essential for the formation of chemically bonded adducts that cause cancer [51]. HOMO and LUMO energies can be used to describe a typical quantum chemical process. In this case, HOMO represent electron energy and energy distribution within the molecule that are least securely bonded, whereas LUMO specifies the shortest route for the addition of additional electrons to the system. Since HOMO is usually linked to a chemical propensity to donate electrons, it is evident that there is a relationship between HOMO and toxicity [52]. However, a molecule's ability to receive electrons is measured by its LUMO energy; the lower the LUMO value, the more likely the molecule is to accept electrons. In this study, the HOMO of the remdesivir with the B3LYP functional in gas medium is -6.4078 eV, whereas the ω B97XD functional yields -8.294 eV. The HOMO values for the two approaches i.e. B3LYP and ω B97XD functionals in the water medium are -6.473 eV and -8.394 eV, respectively. Although the ω B97XD technique yields a comparatively high amount of HOMO energy, both procedures typically provide significant HOMO energy. However, the situation is reversed for LUMO energy (Table 1). It follows from this that the remdesivir is expected to act as a suitable receptor molecule to move low energy electrons to the open molecular

orbital. Figure 3 depicts the HOMO and LUMO orbitals of remdesivir.

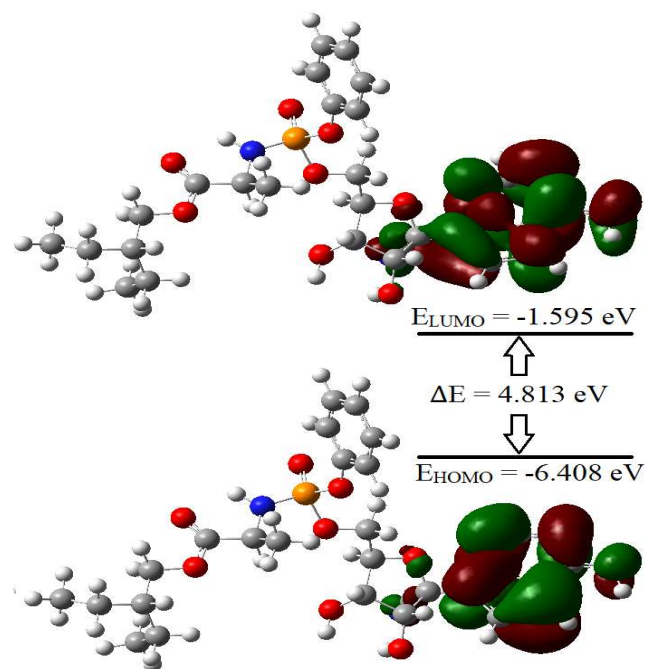
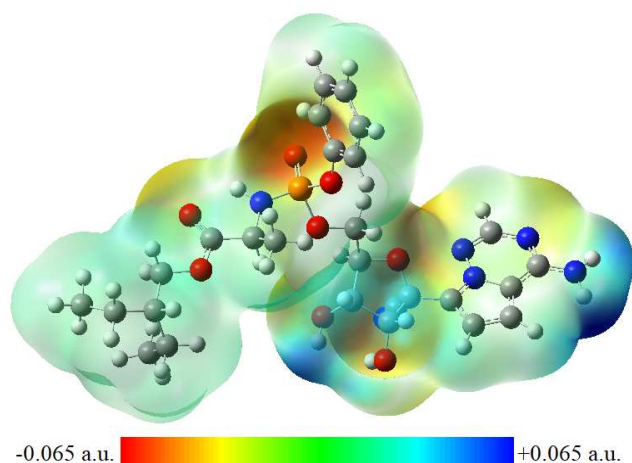


Fig. 3. HOMO and LUMO of remdesivir with B3LYP/6-311+G(d,p) method.

Drug characteristics and their interactions with proteins (or other biological targets) are understood through the use of global reactivity descriptors. The ability to give electrons is shown by the ionization potential energy, whereas the ability to take electrons is indicated by the electron affinity. An important factor in binding is electronegativity, which shows a ligand's capacity to attach to a protein. Water solubility is significantly influenced by a molecule's hardness, which is defined as its resistance to electron donation or acceptance. The opposite of hardness, softness is related to a molecule's ease of accepting or donating electrons and affects its reactivity with protein receptors. The capacity of the medication to interact with biological targets' electron-rich areas is indicated by the electrophilicity index [53]. Global reactivity descriptors of remdesivir are described in detail below, based on the data shown in Table 1. In B3LYP/6-311+G(d,p) method, the drug molecule has a slightly low ionization potential in gaseous medium to that of water medium, which may indicate that it has a greater capacity to give electrons for molecular interactions with nearby protein receptors. The ω B97XD functional gives greater value of ionization potential in both mediums. The electronegativity of studied compound exhibits approximately similar values in both mediums as well as in both techniques. All the remaining parameters are moderately high values in electrophilicity, hardness, softness electron donating and electron accepting capabilities in B3LYP than ω B97XD functional.

Table 1. Electronic and global reactivity descriptors parameters of remdesivir molecule.

Parameters	B3LYP/ 6-311+G(d,p)		ω B97XD/ 6-311+G(d,p)	
	Gas	Water	Gas	Water
Electronic Energy (eV)	-63212.878	-63213.850	-63195.084	-63196.083
Homo energy (eV)	-6.408	-6.473	-8.294	-8.394
Lumo energy (eV)	-1.595	-1.641	0.266	0.193
Energy gap (ΔE) (eV)	4.813	4.831	8.561	8.588
Ionization Potential (I) (eV)	6.408	6.473	8.294	8.395
Electron affinity (A) (eV)	1.595	1.641	-0.266	-0.193
Electronegativity (χ) (eV)	4.001	4.057	4.013	4.101
Electrochemical Potential (μ) (eV)	-4.001	-4.057	-4.013	-4.101
Global Hardness (η) (eV)	2.406	2.416	4.280	4.294
Global Softness (S) (eV ⁻¹)	0.415	0.414	0.233	0.233
Electrophilicity Index (ω) (eV)	3.326	3.407	1.882	1.958
Electron donating Capability (ω^-) (eV)	5.628	5.737	4.423	4.545
Electron accepting Capability (ω^+) (eV)	1.626	1.680	0.410	0.444

**Fig. 4.** MEP map of remdesivir with B3LYP/6-311+G(d,p) method.

Maps of molecular electrostatic potential (MEP) are very helpful for illustrating the distribution of charges and other characteristics linked to charges in molecules. Red is a colour that represents electron-rich region in the MEP map more than other colours and can be attacked by electrophiles. On the other hand, blue serves as a place for nucleophilic assaults and appears as a more appealing molecular area for centres lacking electrons. The average of the two extremes, i.e. red and blue colours, is the mean electron density, which is represented by the green and yellow areas. The red cloud area becomes important in this case because it promotes the development of a strong bond with the protein moiety by means of efficient electron donation. The blue area has the lowest electrostatic potential and weakest interaction to the

protein moiety since it is a poor electron donor. MEP surface of remdesivir has been shown in Figure 4.

To further investigate the absorption (UV–vis) optical spectra, configuration interaction singles (CIS) and TD-DFT calculations have been performed to identify significant electronic transitions between energy levels. UV-visible spectra for high-spin states have also been generated to better understand the nature of low-lying spin excitations. The results indicate that the maximum absorption intensity is confined within the energy range of 4.2–4.9 eV. The absorption spectra of remdesivir as computed by time TDDFT/B3LYP/6-311+G(d,p) method in gas and water mediums have been depicted in Figure 5.

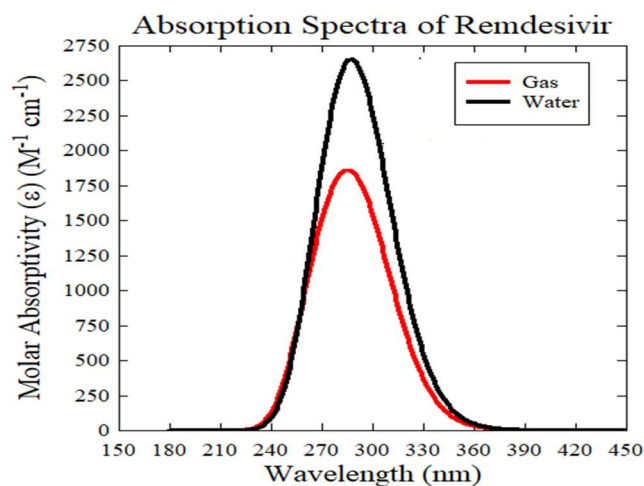
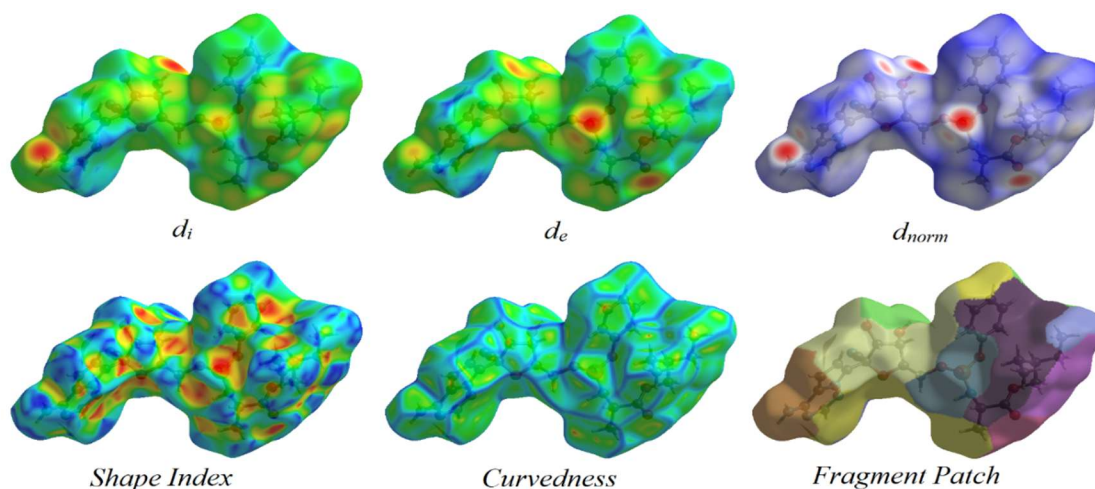
**Fig. 5.** Absorption spectra of remdesivir as computed with B3LYP/6-311+(d,p)

Table 2. Wavelength, energy of excitation and oscillator strength of remdesivir.

Mediums	$\lambda_{\max}$ (nm)	Excitation energy (eV)	Oscillator strength (<i>f</i>)	%MO Contribution
Gas	293.79	4.2202	0.0336	H-2→L (9.6%), H→L (75.7%), H→L+1 (11.7%)
	269.46	4.6013	0.0234	H-2→L (33.9%), H→L (20.0%), H→L+1 (42.4%)
	258.58	4.7948	0	H-1→L (99.9%)
Water	294.52	4.2098	0.0454	H-2→L (11.2%), H→L (73.8%), H→L+1 (12.3%)
	274.6	4.515	0.0297	H-2→L (27.6%), H→L (22.4%), H→L+1 (46.8%)
	251.88	4.9223	0.0001	H-1→L (99.8%)

**Fig. 6.** Hirshfeld surface analysis for remdesivir with d_i , d_e , d_{norm} , shape index, curvedness and fragment patch surfaces.

The Table 2 lists the molecular orbital contributions along with oscillator strength and excitation energy, and absorption wavelength. At absorption wavelength value of 293.79 nm, a strong electronic excitation between HOMO and LUMO (MO contribution: 75.7%) with an oscillator strength of 0.0336 is detected in a gaseous medium. This transition has an excitation energy of 4.220 eV. The second and third ultraviolet bands appear at 269.46 and 258.58 nm, respectively, with excitation energies of 4.601 and 4.795 eV. The intense electronic shift from HOMO to LUMO in the water medium, which accounts for 73.8% of the MO contribution, results in an absorption wavelength of 294.52 nm, an oscillator strength of 0.0454, and an excitation energy of 4.209 eV. Additionally, two more absorption bands have been detected at 274.60 and 251.88 nm, with corresponding oscillator strengths of 0.0297 and 0.0001. The absorption spectra outcome reveals that in both medium, approximately same absorption bands with almost similar excitation energies have been observed.

3.2. Hirshfeld surface analysis

Remdesivir's crystal structure has closed intermolecular atomic contacts, which have been quantified and visualized

using Hirshfeld surfaces analysis. The descriptor normalized contact distance (d_{norm}) is used to map the intensities of intermolecular contacts along with orientations inside the molecular crystal onto Hirshfeld surfaces. Contact distances between the closest atoms within (d_i) and outside (d_e) the surface, respectively, constitute the fundamental basis of the d_{norm} , and expressed as:

$$d_{\text{norm}} = \frac{d_i - r_i^{\text{vdW}}}{r_i^{\text{vdW}}} + \frac{d_e - r_e^{\text{vdW}}}{r_e^{\text{vdW}}}$$

where,

r_i^{vdW} = van der Waals radii of the appropriate atoms internal to the surface

r_e^{vdW} = van der Waals radii of the appropriate atoms external to the surface

Hirshfeld surface maps of remdesivir molecule are shown in Figure 6. The different intermolecular interactions in crystal structure are displayed using Hirshfeld surface (HS) analysis produced by CrystalExplorer17.5 (Figure 7). The interactions O7...H3, O5...H1B, H1B...O5, and H2...N2 are shown by a red patch over the Hirshfeld surface. Intermolecular interactions and their percentage distributions on the Hirschfeld surface are displayed in the two-dimensional fingerprint plots as depicted in Figure 8. As widely dispersed spots of high density because of the

molecule's high hydrogen content, they show that $H\cdots H$ interactions at 49.6% dominate crystal packing, with the tip at $d_e = d_i \approx 1.4$ Å. In the crystal, the distribution of points in the shape of distinctive wings with $d_e + d_i = 2.8$ Å is considered to be the contribution from the $H\cdots O/O\cdots H$ connections (19.7%) between the centroids of the O5–P1 segment and H1B. $H\cdots N/N\cdots H$ (16.4%), $H\cdots C/C\cdots H$

(10.6%), $C\cdots N/N\cdots C$ (1.6%), $C\cdots C$ (1.1%), and $C\cdots O/O\cdots C$ (0.2%) are some additional contributions from the other distinct interatomic contacts to the Hirshfeld surfaces. Further, phosphorus (P1) do not make any contact with neighbouring molecules. The high number of $H\cdots H$ contacts indicates that van der Waals interactions are crucial for maintaining the lattice stability of title compound.

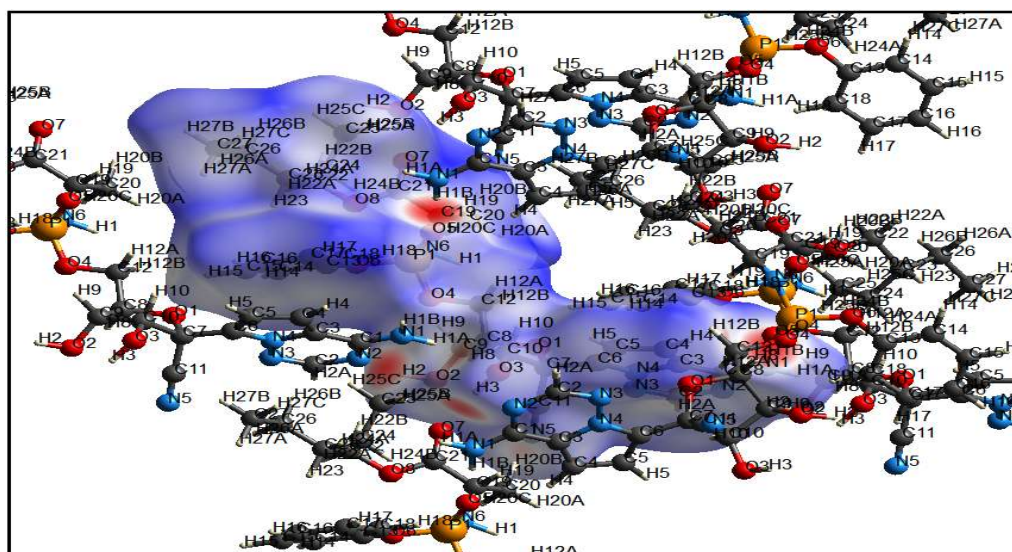


Fig. 7. Close contacts of remdesivir with similar neighbouring molecules in the formation of crystal packing.

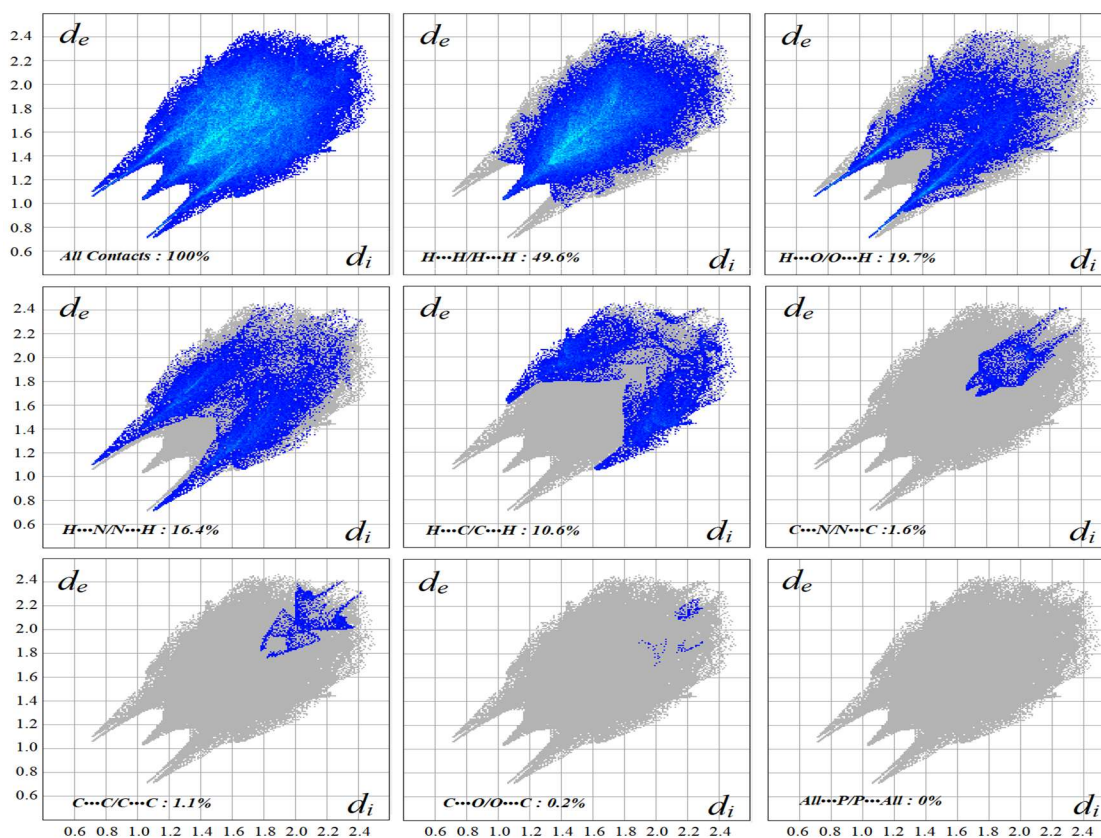


Fig. 8. Different 2D fingerprint plots of remdesivir.

3.3. The 2019-nCoV nsp7-nsp8C complex, Ramachandran plot and molecular docking analysis

The crystal structure of the 2019-nCoV nsp7-nsp8c complex,

with pdb id 6m5i, has been retrieved from the protein data bank [28]. Size-exclusion chromatography (SEC) was used to purify the nsp7+8 complex after it had been produced for crystallization at a stoichiometry ratio of 1:1 [54].

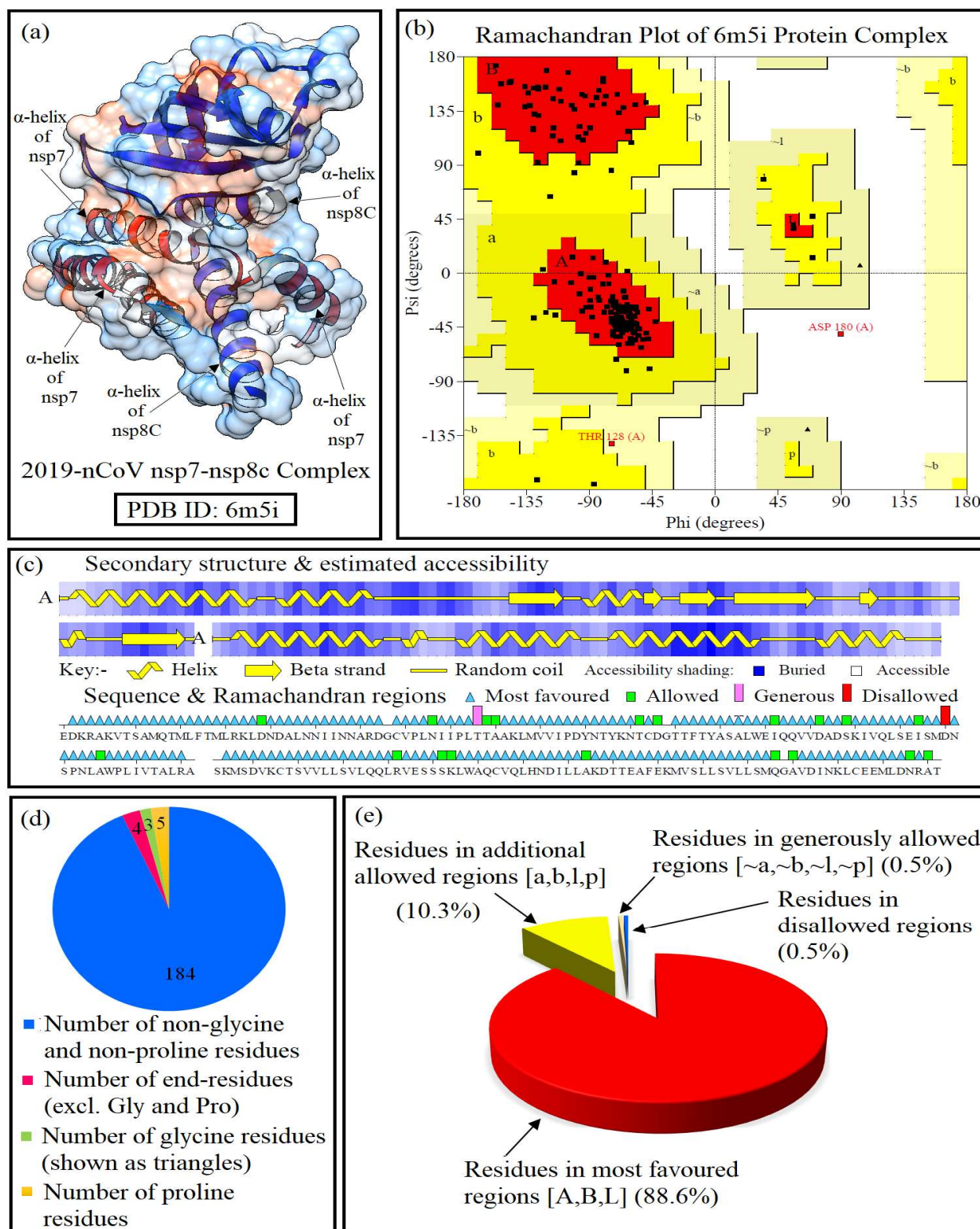


Fig. 9. Structural basis for nsp7+nsp8C SARS-CoV-2 (PDB ID: 6m5i) (a) Residues of the SARS-CoV-2 nsp7+8C complex with ribbon-transparent hydrophobicity surface, (b) Ramachandran map, (c) secondary structure & sequence, (d) number of residue plot and (e) allowed and disallowed region plot.

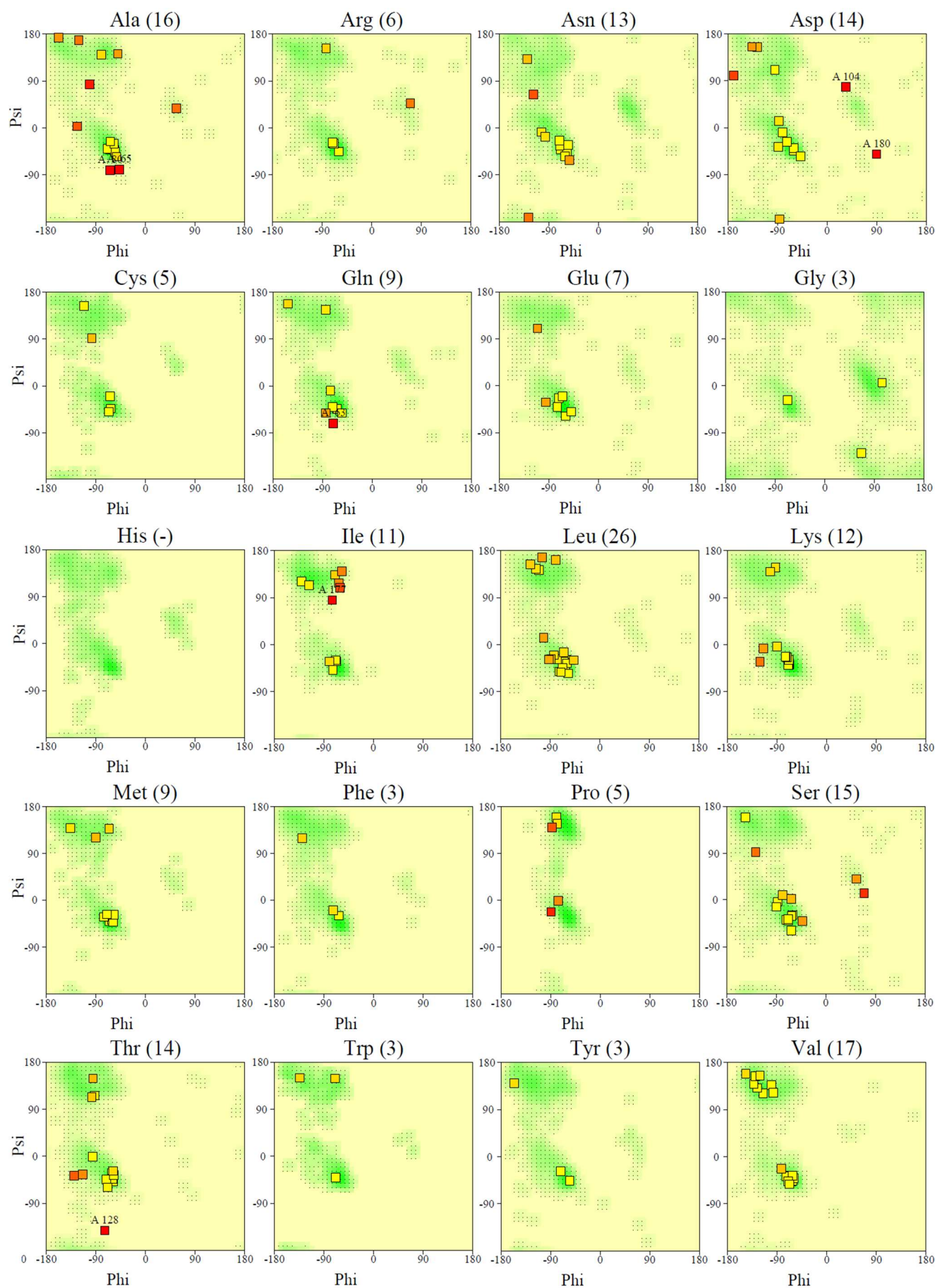


Fig. 10. Ramachandran maps for 20 amino acids in the 6m5i protein.

One copy of nsp7 and one copy of the nsp8C-terminus make up each heterodimer shown in the nsp7+8C complex structure as shown in Figure 9(a). The nsp7 structure consists of four α -helices that form an antiparallel helix bundle. Each of the unit cell's four nsp7 monomers overlays well. In combination with nsp8, nsp7 of the feline coronavirus assumes two distinct conformations, according to a prior investigation. By closely interacting with nsp8C, nsp7 forms a heterodimer with a hidden surface area of $1,467.4 \text{ \AA}^2$, which accounts for $\sim 26.4\%$ of nsp7's total surface area. The protein-protein interaction interfaces are made up of an α -helix bundle with nine hydrogen bonds, four salt bridges, and five α -helices—two from nsp8C and three from nsp7—that interact with one another mostly through hydrophobic interactions (Figure 9(a)). Also, nsp8C has 4 β -strands that are linked by hydrogen bonds between adjacent strands. Figure 9(b) shows that the Ramachandran plot allows for two distinct areas of residue conformations. These correlate to the two most significant secondary structures, the alpha-helix and the beta-sheet, and are represented as the alpha-region and beta-region, respectively. The 6m5i protein has 196 residues, with the most preferred sections (in red) including 163 residues and represented by A, B, and L. As a result, these areas correspond to the beta-strand, alpha-helix, and left-handed alpha-helix conformations. The other permissible areas are represented by a, b, l, and p, which include 19 residues (yellow). The light-yellow tint indicates the shift from the greatest to the least beneficial shape. Figure 9(c) predicts the secondary structure of 6m5i, which includes coiled and β sheet structures, as well as sequence and Ramachandran areas with highly preferred, permitted, generous, and prohibited regions. Figure 9(d) and 9(e) provide the details of number of residues along with allowed and disallowed residue regions. Figure 10 shows individual Ramachandran plots for each of the 20 amino acids. The PROCHECK server [55] has been used to analyse the structural basis of SARS-CoV-2 nsp7+8C, which indicates the permitted and banned locations in respect to protein residue backbone dihedrals.

We used molecular docking to identify the relationship between remdesivir and the SARS-CoV-2 nsp7+8C protein complex. For this purpose, molecular docking has been used to investigate the mechanism of action of remdesivir. The remdesivir and target protein were then prepared for docking investigations using the SwissDock web service. Molecular docking studies found that remdesivir has a high binding affinity to the target receptor involving SER90 of the α -helix of nsp8C and GLU74 of the α -helix of nsp7 residues, which are roughly $1.957 \text{ \AA}$ and $2.026 \text{ \AA}$ from the ligand. The binding energy and FF score corresponding to this pose are -9.133 and $-1177.067 \text{ kcal/mol}$ respectively. Other binding sites have also been identified between protein residues and ligand. The findings of this study are important for understanding remdesivir's mechanism of action on the SARS-CoV-2 protein receptor. It will also give information on future studies aimed at developing alternate toxicity treatments. Figure 11 illustrates the remdesivir-protein complex's optimal binding pose, while Figure 12 displays the free

energy components for this pose.

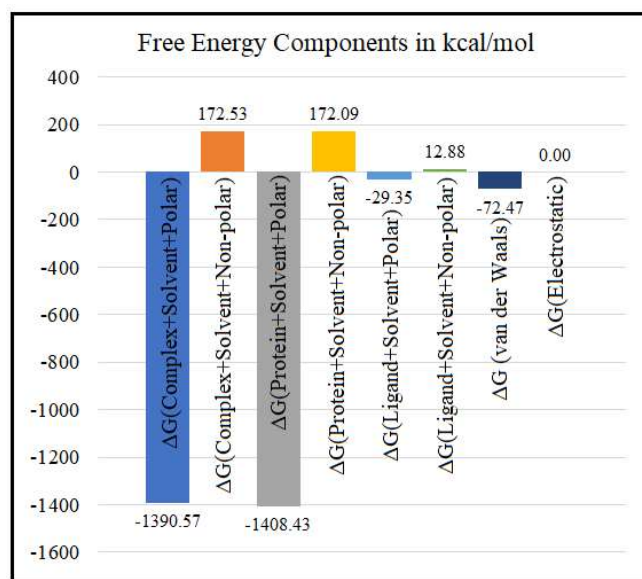


Fig. 12. Free energy components of remdesivir-nsp7+nsp8C SARS-CoV-2 complex for best docking configuration.

3.4. Molecular dynamics simulation of remdesivir- SARS-CoV-2 nsp7+8C protein complex

A 100 ns MD simulation has been run to investigate the remdesivir's steric refinement and stability with SARS-CoV-2 nsp7+8C protein complex. For this, the optimal binding posture of the protein-ligand complex has been chosen, and the MD simulation has been initiated using the NAMD tool. Following the MD simulation, trajectory data were generated, and several analyses were done, including RMSD, RMSF, radius of gyration (R_g), hydrogen bond interactions and SASA changes, as well as electrostatic and van der Waal's energy fluctuations.

3.4.1. The RMSD and RMSF analysis

The deviation in the protein's backbone throughout the 100 ns simulative period is calculated using the root mean square deviation, or RMSD, value. Both the complex and the protein fluctuate as the temperature rises and then stabilize. Throughout the simulation time, the protein and complex remained rather constant and nearly overlapped. The protein RMSD initially varied from 0 to $2.1 \text{ \AA}$ up to 3 ns in the SARS-CoV-2 nsp7+8C protein complex in a complex with remdesivir before stabilizing (Figure 13). The protein-ligand complex also follows approximately the same trend as that of protein's RMSD with stabilization at the mean value of $2.0 \text{ \AA}$. As a result, the RMSD value would be associated with substantial stability, meaning that the conformation of studied molecule has not changed. Thus, for the complex, the total RMSD is stable and hence is acceptable.

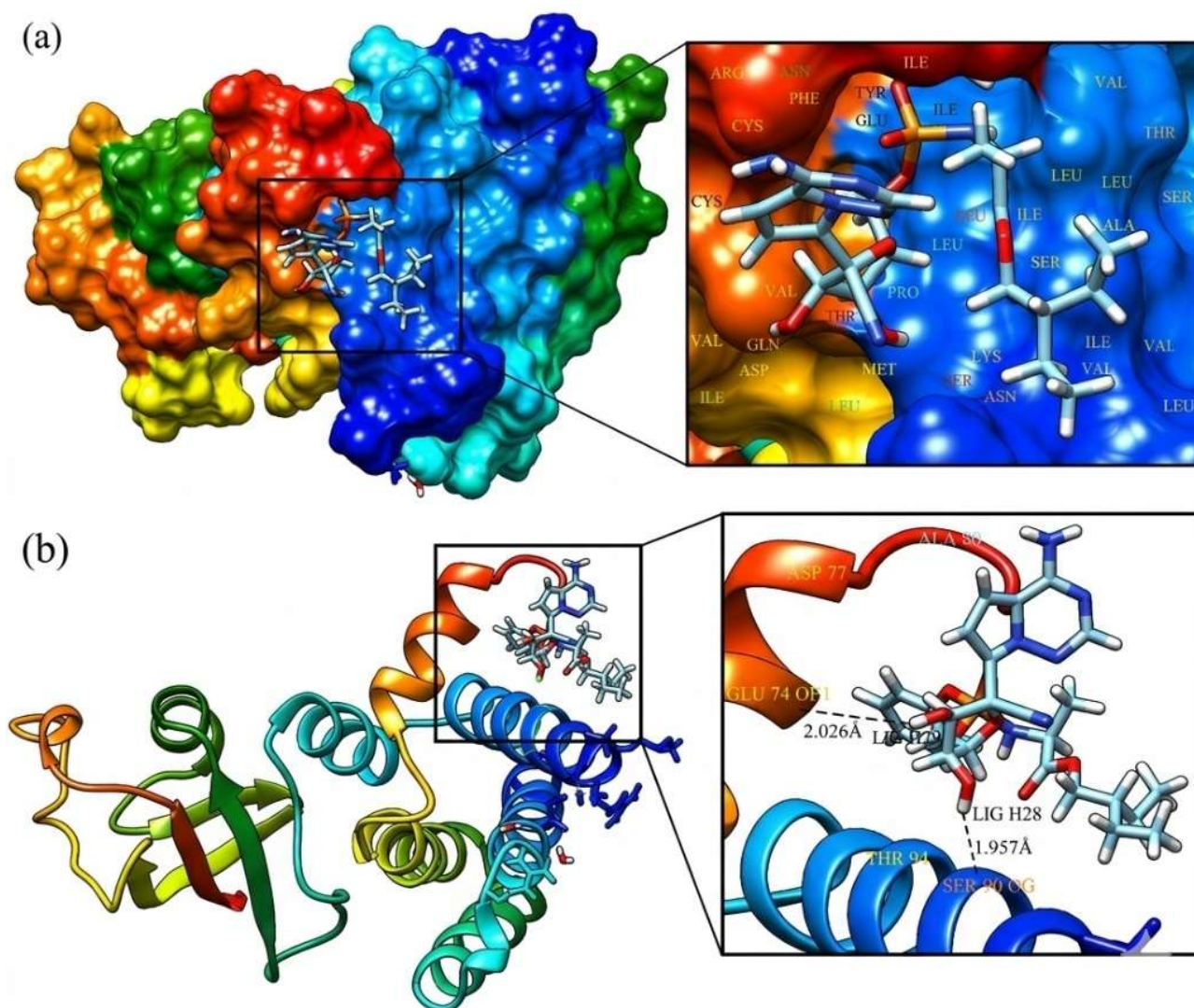


Fig. 11. The ideal nsp7+nsp8C SARS-CoV-2 (PDB ID: 6m5i) binding configuration for remdesivir with (a) hydrophobicity surface and (b) ribboned.

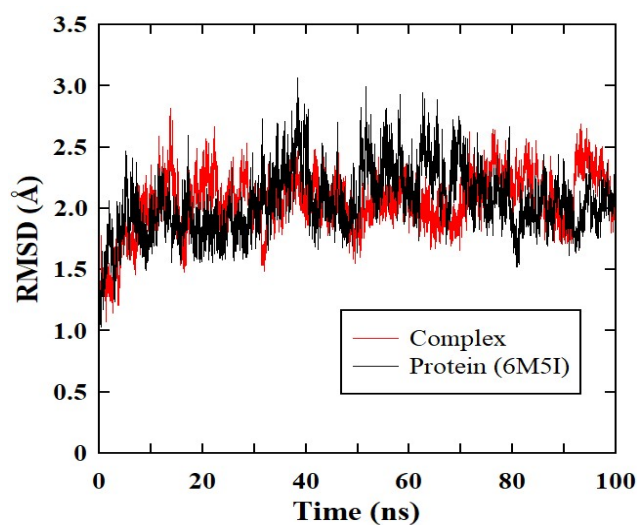


Fig. 13. RMSD of remdesivir-nsp7+nsp8C SARS-CoV-2 complex.

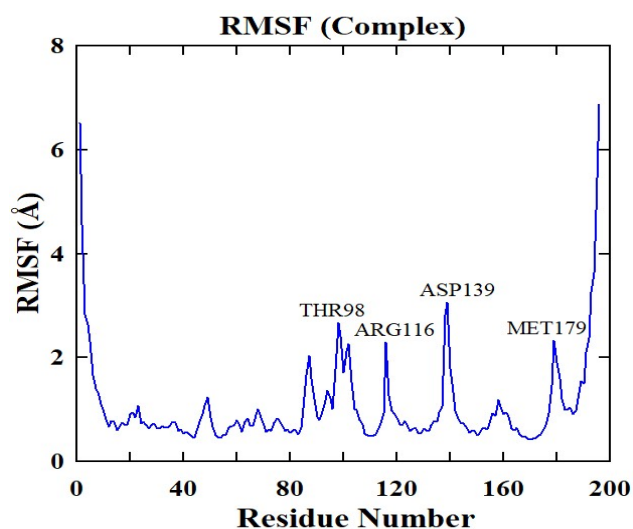


Fig. 14. RMSF of remdesivir-nsp7+nsp8C SARS-CoV-2 complex.

The RMSF value of the remdesivir-SARS-CoV-2 nsp7+8C protein complex is calculated to see if the inhibition of the ligand has any effect on the dynamic behaviour of the residue. The complex exhibits a variety of vibratory behaviours, as seen in Figure 14. Residues THR98, ARG116, ASP139, and MET179 appear to show greater variations than the other residues, with values of 2.66 Å, 2.29 Å, 3.00 Å, and 2.33 Å, respectively. For small proteins, a fluctuation value less than 2.0 Å is deemed acceptable. Therefore, RMSF analysis indicates that there is some conformational diversity among the amino acids in the complex's protein.

3.4.2. The radius of gyration and SASA analysis

The radius of gyration (R_g) has been tracked during the course of the MD trajectory using the NAMD tool in order to obtain more understanding of the complex stability under investigation. A collection of atoms' mass-weighted root mean square deviation (RMSD) with respect to their common centre of mass is represented by R_g , the stability parameter that takes into consideration the global stability of either the ternary structure of a ligand or protein [56]. As a result, the illustrated low R_g values reaching a plateau around an average value would suggest the examined molecule's persistent stability or compactness. The investigation provided evidence of the remdesivir-6m5i complex's favoured stability, as demonstrated by the somewhat lower R_g tones achieved in comparison to the 6m5i protein (Figure 15).

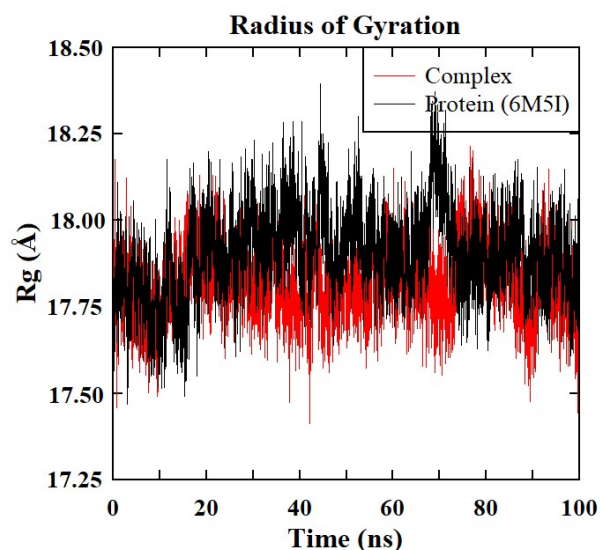


Fig.15. Radius of gyration of remdesivir-nsp7+nsp8C SARS-CoV-2 complex.

The simulation routes for the MD run of the chosen ligand indicate that the residues of amino acids are constant during the simulation, as seen by the clear variations of R_g for the complex, which stay consistent throughout the whole

simulation period with a mean value of 17.84 Å. The SARS-CoV-2 nsp7+8C protein complex also follow the same trend with slightly greater R_g value (12.02 Å). Consequently, the result indicates that there is no appreciable variation between the complex's initial and final values. It may therefore be determined that the stiffness of the protein backbone associated with the ligand.

An analysis of the degree to which remdesivir covered the 6m5i binding site in the SARS-CoV-2 nsp7+8C protein complex has been conducted in order to conjecture the potential of tiny ligand inhibitor accommodating the 6m5i-remdesivir binding site. The solvent-accessible surface area (SASA) of the binding region in the presence and absence of ligand has been studied using the MD run. SASA often corresponds with the molecular surface area that solvent molecules may measure, giving rise to a quantitative assessment of the degree of solvent/protein interaction [57]. The SARS-CoV-2 nsp7+8C protein complex binding site atoms were analyzed using spherical probes to estimate the solvent-exposed area of the lining residues. Figure 16 displays the SASA value for the protein-ligand combination that was computed over time. The SASA plots for the protein and complex almost overlap and show early decrease until 8 ns, increase until 32 ns, and continued stabilization with a mean value of 11654 Å² throughout the simulation step. This means that the complex's stable SASA result closely matches the RMSD and radius of gyration results.

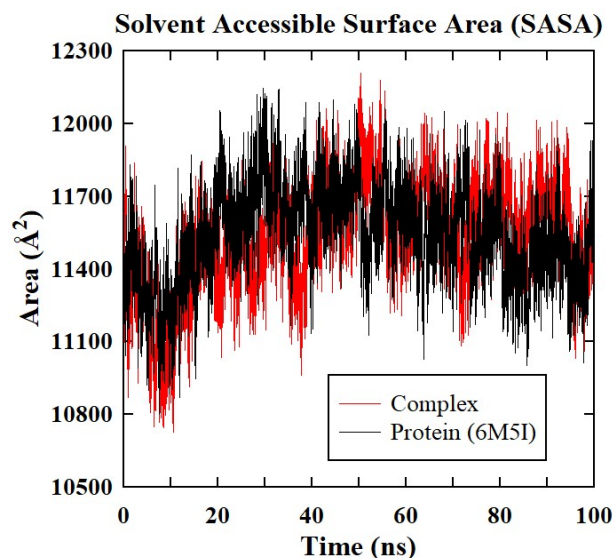


Fig. 16. SASA fluctuations for 100 ns of simulation.

3.4.3. The H-bond interaction and binding free energy analysis

To comprehend the observed conformational changes and stability of the ligand-protein complex, it was thought to be essential to examine the hydrogen bond network connections between the 6m5i residues and remdesivir during the 100 ns MD simulation. The preservation of protein structure is

heavily reliant on hydrophobic interactions and hydrogen bonds. The entire quantity of hydrogen bonding within complex has been determined (Figure 17). The remdesivir-6m5i complex exhibited stable intermolecular hydrogen bonds with a mean value of 45, as shown in Figure 17(a). The complex between the residues THR142 and ASP139 shows hydrogen bonding spanning from 0 to 2, with a maximum occupancy of 81.05%, as can be shown in Figure 17(b). The donor-acceptor occupancies for the H-bonding between residues ARG116-ASP117 and ILE137-LEU189 have been determined to be 73.67% and 66.58%, respectively, for the same range. There is a hydrogen bonding between residues LEU122 and MET134 that has a donor and acceptor occupancy value of 68.06% and a range of 0 to 1. Remdesivir therefore has a potential role in blocking SARS-CoV-2/host entry, as evidenced by the shown presence of hydrogen bonding between remdesivir and protein residues for more than complete steps.

We investigated the differential binding affinities for the protein chain and the ligand of interest by displaying the accessibility of the preferred site. In light of this, the binding-free energy calculation that follows was used to investigate the remdesivir-receptor binding site affinity, comprehend the nature of the drug-protein binding, and gather further information on residue contribution. For the designated binding-free energy calculations, which are performed using the NAMD program, the MD-based MM/GBSA technique has been used. Generally speaking, the trajectories of the MD simulation that show stable protein-ligand complex should be used to determine the binding-free energy. In order to calculate each energy period, representative frames were selected, preserved, and the free energy computation has been applied during the 30–70 ns and final 20 ns intervals. The results suggest a polar environment surrounding the

binding site, with all compounds having electrostatic energies larger than van der Waals energies. Van der Waals energy has the corresponding average values of -395.31, 25.61, and -373.90 kcal/mol, whereas the average values of electrostatic energy of protein, ligand, and complex are -6286.25, -8.14, and -6299.79 kcal/mol. Remdesivir-6m5i complex, has a binding free energy of -9.6 kcal/mol, indicating that hydrophobic and H-bond interactions are the main ways the ligand interacts with the residue's active site. Figure 18 shows the van der Waals energy and electrostatic trajectories of the protein, ligand, and complex. Furthermore, a number of important residues that were involved in pertinent aspects of the first docking study demonstrated noteworthy contributions to the computed ΔG .

4. CONCLUSIONS

This paper reports ab-initio approach of remdesivir drug along with its inhibition activity against SARS-CoV-2 nsp7+8C protein complex. The toxicity and electrophilic/nucleophilic sites of the remdesivir molecule are clearly detailed by the HOMO-LUMO and MEP surfaces. Absorption spectra of the drug molecule elicit its UV sensitivity. According to Hirschfeld surface analysis, a high number of H...H connections suggests that van der Waals interactions are essential to preserving the title compound's lattice stability. The skeletal structure of the protein model is supported by the Ramachandran plot. Strong binding affinity of remdesivir to the target receptor, which involves SER90 of the α -helix of nsp8C and GLU74 of the α -helix of nsp7 residues, has been discovered by molecular docking studies.

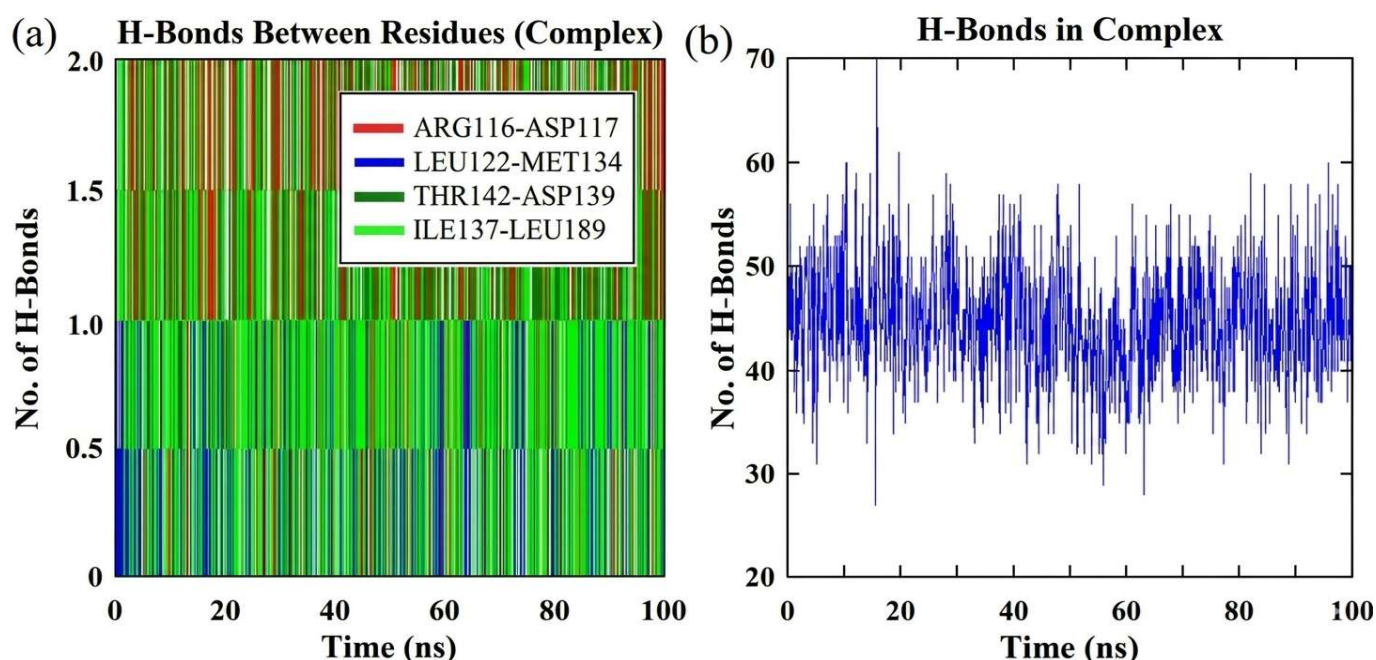


Fig.17. Hydrogen bond interactions (a) Between remdesivir and selected residues of 6m5i and (b) complete.

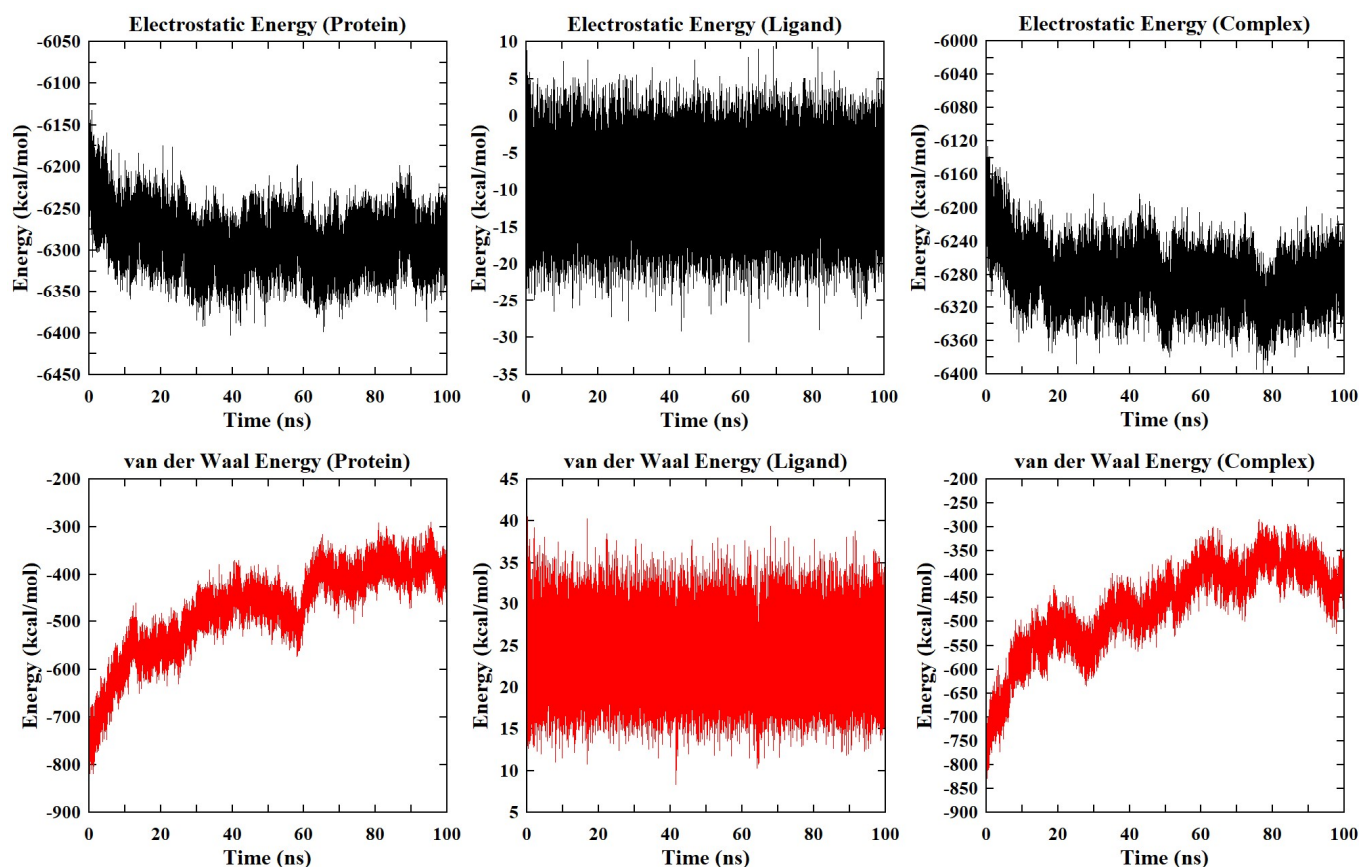


Fig. 18. The protein (6m5i), ligand (remdesivir), and protein-ligand complex electrostatic and van der Waal energies during 100ns MD simulation.

The stability of the complex is demonstrated by the examination of the RMSD and RMSF analysis. The radius of gyration analysis suggests that the protein remains the folded and hence the drug remdesivir does not destabilize the structure of the protein. The complex's SASA analysis supports the RMSD, RMSF, and Rg results. The protein-ligand complex's hydrogen bond trajectories indicate that remdesivir and the 6m5i residues have a strong hydrophobic contact. According to the binding free energy determined by the MM/GBSA technique, remdesivir has high binding stability and affinity with the SARS-CoV-2 nsp7+8C protein complex. The development of future COVID-19 outbreak prevention therapy alternatives is also made possible by this work.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

Availability of data and material

All of the data obtained or analyzed during this study is included in the report that was submitted.

Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for the content and writing of this article.

Authors' contributions

All authors contributed equally to this work.

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