

# Target SARS-CoV-2: Computation of Binding energies with drugs of Dexamethasone/Umifenovir by Molecular Dynamics using OPLS-AA force field

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## Research Article

**Keywords:** SARS-CoV-2 protein, Dexamethasone, Umifenovir, molecular dynamics, Gromacs, Gibb's free energy, Interactions.

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## Target SARS-CoV-2: Computation of Binding energies with drugs of Dexamethasone/Umifenovir by Molecular Dynamics using OPLS-AA force field

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### *Abstract*

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Molecular Dynamics simulation using Gromacs with OPLS-AA force field is performed for 100ns between SARS-CoV-2 main protease and Dexamethasone / Umifenovir drugs at 300 K/1 atm pressure. The trajectory of Root Mean Square Deviation (**RMSD**) and Radius of Gyration(**Rg**) emphasized the achievement of equilibrium and compactness. The drug-binding affinities on SARS-CoV-2 main protease are estimated via MM/PBSA method. The sign with magnitude of computed Gibbs free energy indicated the presence of strong interactions between SARS-CoV-2 and drugs of Dexamethasone / Umifenovir. The study revealed that the drug Dexamethasone is more effective over Umifenovir in binding SARS-CoV-2 main protease.

**Key words:** SARS-CoV-2 protein, Dexamethasone, Umifenovir, molecular dynamics, Gromacs, Gibb's free energy, Interactions.

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## **1. Introduction:**

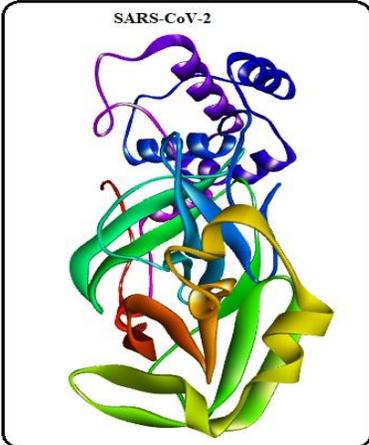
Coronavirus disease (COVID-19) is an infection causing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a recently revealed novel coronavirus. SARS-CoV-2 is genetically different from viruses that trigger influenza. These are encased, single-stranded RNA viruses whose exterior is enclosed by a halo of protein spikes (corona). The SARS-CoV-2 fit in to the cysteine protease family and the fatality due to this has reached thousands and been mounting step by step, which is a major crisis in the world [1-3]. Since SARS-CoV-2 is rapidly spreading worldwide, World Health Organization (WHO) has declared it as a pandemic disease[4]. Consequently, the challenge to search for medicines to prevent novel corona virus is of immense concern for all scientists around the globe.

Governments and pharmaceutical companies are paying attention on probing and developing the unambiguous vaccine or antiviral drug to avert or manage budding infection of SARS-CoV-2. On the other hand, such selections need much time for the developing procedure. Drug repurposing permits to quickly examine medical management, at lower costs and with diminished danger of disappointment as the wellbeing profile of the medication is commonly entrenched. Growing new medications is clearly a protracted procedure, in this way unfeasible to confront the prompt worldwide crisis. At present, anti-retroviral drugs are under clinical advancement based on earlier achievement of the therapeutic management pertinent to viruses of SARS-CoV and MERS-CoV [5-7]. Thus, the aim of this investigation is to explore and distinguish the binding affinities and interactions of certain drugs against the main protease of SARS-CoV-2 utilizing computational and measurable tools.

It is to be noted that the viruses need host-cell functional receptors in humans to accumulate and attack the immune system. As per the studies [8,9], the spike protein SARS-CoV-2 attacked the Angiotensin-converting enzyme 2 (ACE2) target protein on the surface of pulmonary epithelial cells of human [10,11].

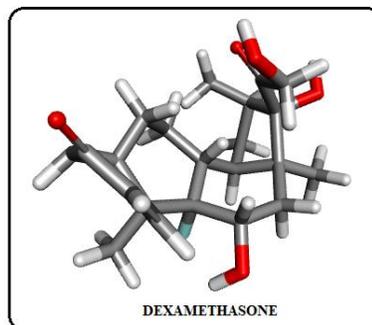
In the present study, 6M03 main protease pertinent to SARS-CoV-2 is considered as the attractive drug target for the healing of SARS-CoV-2 infection and hence we are going to explore the binding capacity of Dexamethasone and Umifenovir drugs as ligands directly to the PDB6M03 pertinent to the structure of SARS-CoV-2 main protease via molecular dynamic studies using Gromacs with

OPLS-AA force field. The sources from which SARS-CoV-2 main protease in apo form, drugs of Dexamethasone/Umifenovir taken with their structures are shown in **Table 1**.

Protein/Drug	Structure	Source
SAS-CoV-2 (main protease in apo form)	 A 3D ribbon diagram of the SARS-CoV-2 main protease structure. The structure is shown in a multi-colored ribbon representation, with different regions highlighted in purple, blue, green, yellow, and orange. The protein is a complex, multi-domain structure with several alpha-helices and beta-sheets. The label "SARS-CoV-2" is visible at the top of the structure.	<a href="https://www.rcsb.org/structure/6M03">https://www.rcsb.org/structure/6M03</a>

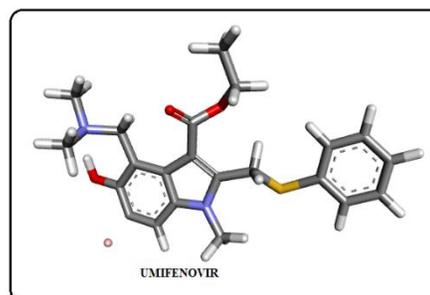
Dexamethasone drug [C<sub>22</sub>H<sub>29</sub>FO<sub>5</sub>]

<https://www.drugbank.ca/drugs/ DBCAT000963>



Umifenovir drug[C<sub>22</sub>H<sub>25</sub>BrN<sub>2</sub>O<sub>3</sub>S]

<https://www.drugbank.ca/drugs/DB13609>



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**Table 1.** Target SARS-CoV-2 main protease in apo form with various drugs (ligands) used in present study of molecular dynamics

The information concerning interaction mechanisms of a drug with SARS-CoV-2 protein is requisite to know the drug's pharmacodynamics and pharmacokinetics[12]. To the best of our knowledge, this is the first report for estimation of the Gibbs free

energy of the Dexamethasone and Umifenovir drugs on the main protease (PDB6M03) of SARS-CoV-2 using molecular dynamic simulations by Gromacs with OPLS-AA force field. The results of this study show that the Dexamethasone and Umifenovir are considered as a valuable resource recommended for attacking SARS-CoV-2 protein. The inhibit action of Dexamethasone and Umifenovir drugs on ACE2 is already proved [13,14].

Drug Umifenovir is considered as an vital drugs for the treatment of HIV. Dexamethasone is a corticosteroid used in a extensive variety of conditions for its anti-inflammatory and immunosuppressant results. It became tested in hospitalized sufferers with COVID-19 inside the UK clinical trial recuperation and became observed to have benefits for significantly unwell sufferers. consistent with preliminary findings shared with WHO, for sufferers on ventilators, the remedy was proven to lessen mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth respectively [15]. It is our hope that as a minimum, this work can be helpful for future design or development of more specific inhibitors for the treatment of SARS-CoV-2 infection.

## **2.Theory:**

### **2.1. Biothermodynamics of protein-drug complex :**

Application of thermodynamics in biochemical engineering to rationalize bioprocess development and obviate a substantial fraction of this need for tedious experimental work. The understanding over thermodynamics are employed in choosing a drug(ligand) as it interact, bind and control the function of biological receptors (protein) that helps to cure a disease. The main point in this is to evaluate the change in Gibbs free energy ( $\Delta G_{\text{bind}}$ ). This change in Gibbs free energy includes various interactions, such as van der Waals, hydrogen bonds, electrostatic and hydrophobic interactions. According to thermodynamics,  $\Delta G_{\text{bind}}$  determines the stability of any given protein ligand complex, or, alternatively, the binding affinity of a ligand to a given acceptor [16,17]. Moreover, the protein ligand association extent is determined by the magnitude of the negative  $\Delta G_{\text{bind}}$ . The negative values with high magnitude show a strong binding between ligand and protein. To explore binding affinity ( $\Delta G_{\text{bind}}$ ), MM/PBSA method is outlined below:

The Gibb's free energy( $\Delta G_{\text{bind}}$ ) is given by

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

where,  $G_{\text{complex}}$  is the whole free energy of the protein-ligand system and  $G_{\text{protein}}$  and  $G_{\text{ligand}}$  are the gross free energies of the protein and ligand. The value of  $G_{\text{protein}}$  or  $G_{\text{ligand}}$  is evaluated by

$$G_x = E_{\text{MM}} - (TS) + (G_{\text{solvation}})$$

where,  $E_{\text{MM}}$  is the average molecular mechanics potential energy in vacuum.  $(TS)$  denotes the product of the temperature and the entropic contribution and  $(G_{\text{solvation}})$  is the free energy of solvation. Further,

$$E_{\text{MM}} = E_{\text{bonded}} + E_{\text{non-bonded}} = E_{\text{bonded}} + (E_{\text{vdW}} + E_{\text{elect}})$$

where,  $E_{\text{bonded}}$  is bonded interactions and  $E_{\text{non-bonded}}$  includes (h-bond, hydrophobic) van der Waals' ( $E_{\text{vdW}}$ ) and electrostatic ( $E_{\text{elect}}$ ) interactions and are modeled using a Lennard- Jones (LJ) and Coulomb potential function, respectively.

$G_{\text{solvation}}$  (solvation free energy) is given by:

$$G_{\text{solvation}} = G_{\text{polar}} + G_{\text{non-polar}}$$

here,  $G_{\text{polar}}$  and  $G_{\text{non-polar}}$  are the electrostatic and non-electrostatic contributions to the solvation free energy, respectively.  $G_{\text{non-polar}}$  includes attractive and repulsive forces between solvent and solute that are generated by van der Waals' interactions and cavity formation, respectively. Furthermore,

$$G_{\text{non-polar}} = G_{\text{cavity}} + G_{\text{vdW}}$$

We used solvent accessible surface area (SASA) for computation of free energy of solvation pertinent to non-polar model. In the end, average binding energy, average van der Waals' and electrostatic energies as well as polar solvation(PS) and SASA non-polar energies were calculated for each system.

In this study, we adopted `g_mmpbsa` tool for the computation of  $\Delta G_{\text{bind}}$ . The evaluation of different energies by `g_mmpbsa` tool is available in the references[18-22]. Precisely, in MM/PBSA method, the enthalpy of the system is calculated using the molecular mechanics(MM) method; the contribution of the polar part and nonpolar part of the solvent effect to the free energy is determined by solving the Poisson-Boltzmann (PB) equation and calculating the molecular surface area (SA), respectively.

## **2.2. Molecular dynamics (MD) simulation in Biothermodynamics:**

Molecular dynamics (MD) simulation is a computational method to enables us to calculate movements of atoms in a molecular system by numerically solving Newton equations of motions [23]. In MD, one usually look for a ligand which can bind easily with desired protein leading to the negative Gibbs Free Energy. Parameters of mathematical functions describing the potential energy of a system, termed the force field, are set to simulate the movements of atoms and molecules[24]. OPLS-AA (Optimize Potential for Liquid systems-all atom) is the most widely used biomolecular force field and is the latest and better force fields over others when ligands are to be included[25]. Hence we used the OPLS-AA force fields on (SARS-CoV-2+Dexamethasone) and (SARS-CoV-2+Umifenovir).

The method fabrication in understanding of binding energetics between protein-Ligand interactions with the aid of thermodynamics and is recently used to assist in the discovery, development of antiviral drugs [26] and computer-aided design of drug molecules(CADD).

$\Delta G_{\text{bind}}$ .

In the present context, Molecular Dynamics study is performed with Gromacs-2020.1 on Ubuntu platform. The molecular mechanics Poisson-Boltzmann surface area (MM/PBSA) method needs the trajectories generated by GROMACS (`g_mmpbsa`) [27-29] to calculate the  $\Delta G_{\text{bind}}$  between the SARS-CoV-2 receptor and Dexamethasone and Umifenovir.

## **2.3 Preparation of SARS-CoV-2 + Dexamethasone / Umifenovir:**

The molecular dynamic simulation is followed as per the usual standard operating procedure (SOP)[30]. The SARS-CoV-2 main protease biological target is the PDB6M03 protein presented at RCSB Protein Data Bank [31]. The structure of the protease was

optimized and checked by Swiss-PDB viewer software packages (version 4.1.0) in light of their minimum energy. Some noteworthy components, for example, bond order, side chain geometry, and missing H-bonds, were seen in the structure of the protease. PyMol (version 1.1) software package was utilized to eradicate all the hetero atoms, H<sub>2</sub>O, and inhibitor present in the structure [32]. This protein at pH = 7.4 is optimized by using Avagadro software with the purpose to correct the mismatch values of bond lengths, bond angles, bending angles, and unusual nonbonding interactions due to the atoms in different parts of the compounds occupying the same space. The OPLS-AA force field was utilized for this molecular dynamics to depict the macromolecular framework. Later, the protine energy is minimized with Gromacs. This structure is finally used for simulation. The chemical structures of Dexamethasone and Umifenovir were downloaded from the drugbank (<https://www.drugbank.ca/>) database. Later, Dexamethasone and Umifenovir drug files were prepared and optimized using Avagadro software and converted to the executable OPLS-AA topology files [33]. Later, their energy is minimized with Gromacs tool. The minimized structure is finally used for simulation. With Gromacs-2020.1, executable files of SARS-CoV-2 protein were created with OPLS-AA force field. In a cubical box (d = 1nm), the executable files of protein-ligands are combined, solvated and neutralized respectively. The initial MD simulation is energy minimized by using steepest descent. This immediately followed by the equilibration of simulation box in NVT ensemble. The temperature of system was relaxed for 20 ns using modified Berendsen thermostat with a relaxation time of 2 fs and a reference temperature of 300 K. Temperature relaxation was followed by pressure relaxation of the simulation box in NPT ensemble for 40 ns. Pressure equilibration was achieved using Berendsen barostat. A relaxation time of 2 fs and reference pressure of 1 atm was used in pressure relaxation of simulation box. Leapfrog algorithm was used during simulation to integrate the equation of motion. Long-range electrostatic interactions were accounted during simulation by Particle mesh Ewald method. During simulation, a spherical cut-off of 1.2 nm was used for both electrostatic and van der Waals forces. Upon completion of NVT and NPT equilibrations, final MD simulations have been carried for 100ns and observed that the complexes are equilibrated, stabilized well below 10 ns and a relaxation time of 2 fs with reference temperature at 300 K and pressure of 1 atm using modified Berendsen thermostat and Parrinello-Rahman barostat respectively. All the bond lengths were limited by the LINCS

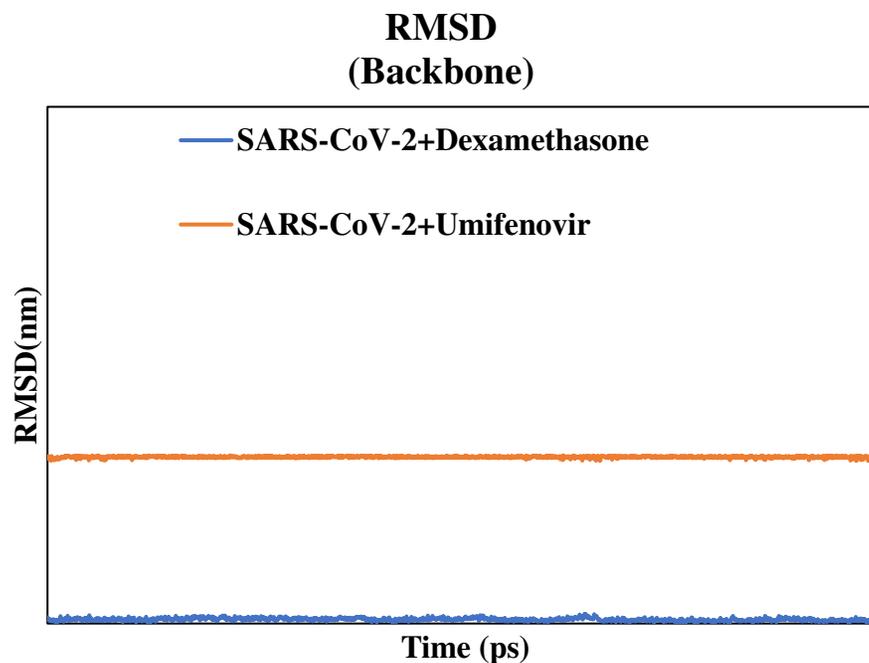
algorithm. The electrostatic interactions were calculated using the Particle Mesh Ewald (PME) summation Scheme [34] and the conformations were stored every 20 ps.

### **3. Result analysis:**

#### **3.1. Analysis of MD trajectories:**

Root-mean-square deviation (RMSD) and radius of gyration (Rg), from the MD simulations using the GROMACS routines. The graphs related to **RMSD** and **Rg** properties are widely used in predicting the structural activity of a protein molecule [35].

**i) RMSD of the trajectory of the SARS-CoV-2 backbone:** The stabilities of the trajectories for (SARS-CoV-2+Dexamethasone) and (SARS-CoV-2+Umifenovir) were examined (**Graph 1**) using the RMSD for the backbone of SARS-CoV-2.

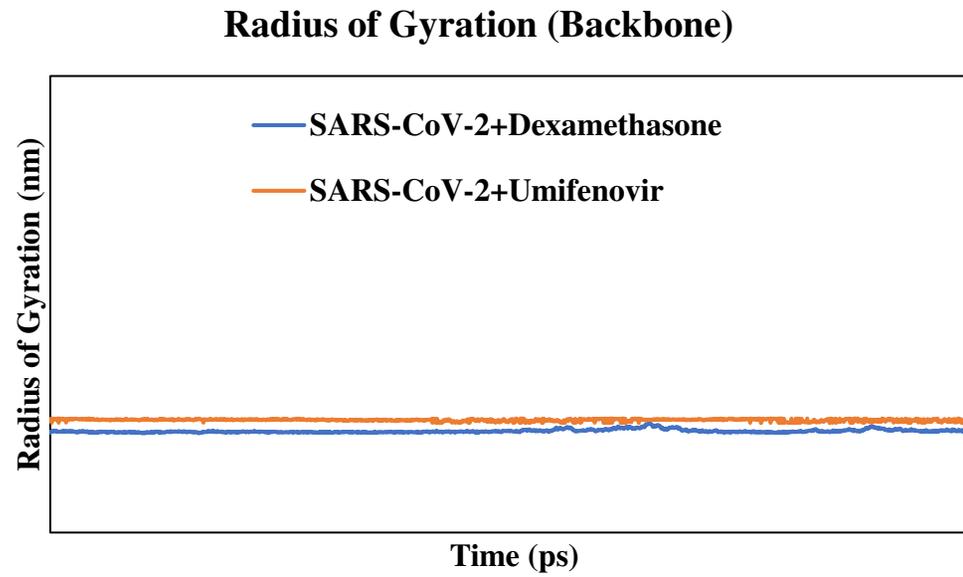


**Graph1.** RMSD graph for backbone of (SARS-CoV-2+Dexamethasone) and (SARS-CoV-2+ Umifenovir) systems.

The **Graph1** shows that the RMSD of the systems fluctuated around 1/6 nm for (SARS-CoV-2+Dexamethasone)/(SARS-CoV-2+Umifenovir) and reached equilibrium from initial stages of md run respectively. This clearly indicates that the systems were equilibrated well and the root mean square deviation had only low fluctuations around their mean values.

**ii) Radius of gyration of the trajectory of the SARS-CoV-2 backbone:** The radius of gyration (Rg) speaks about the structure compactness. The lower level of vacillation with its consistency all through the recreation demonstrates the more noteworthy

compactness and unbending nature of a framework. Thus, if a protein is stably folded, it will likely maintain a relatively steady value of radius of gyration. The Radius of gyration for the systems were computed and drawn as **Graph 2** against simulation time to study the protein compactness. The study values in graph clearly showed that the systems stabilized properly and achieved compact structures [36,37].



**Graph 2.** Radius of Gyration graph for backbone of (SARS-CoV-2+Dexamethasone) and (SARS-CoV-2+Umifenovir) systems.

### 3.2 Predicted inhibitory efficiency:

The interaction strengths of bonded and non-bonded for the whole system (with solvent) under study is evaluated under certain heads and finally summed up to the total binding energy in MM/PBSA. The susceptibility of Dexamethasone and Umifenovir towards the SARS-CoV-2 protein is estimated using the MM/PBSA approach on 100 snapshots extracted from the last 20 ns of simulation. The

MM/PBSA results are tabulated in **Table 2**. From table, van der Waals ( $\Delta_{vdW}$ ) interaction energy: (SARS-CoV-2+ Dexamethasone) > (SARS-CoV-2+Umifenovir), Electrostatic interaction energy ( $\Delta_{Elect}$ ) follow: (SARS-CoV-2+ Dexamethasone) > (SARS-CoV-2+ Umifenovir),  $\Delta_{PS}$  interaction energy follow: : (SARS-CoV-2+ Dexamethasone) > (SARS-CoV-2+ Umifenovir),  $\Delta_{SASA}$  energy follow: (SARS-CoV-2+ Dexamethasone) > (SARS-CoV-2+ Umifenovir). Finally, the binding energy ( $\Delta G_{bind}$ ) follow: (SARS-CoV-2+ Dexamethasone) > (SARS-CoV-2+ Umifenovir).

Therefore,  $\Delta G_{bind}$  of Dexamethasone is approximately 1.5 times of  $\Delta G_{bind}$  of Umifenovir. This result shows that Dexamethasone drug can clinically boost efficacy in fight against SARS-CoV-2 infection in humans over Umifenovir via its strong binding affinity. Thus this result pave a way for the usage of these drugs (Dexamethasone and Umifenovir) as clinical trial on SARS-CoV-2 infection.

System	$\Delta_{vdW} \pm SEM$	$\Delta_{Elect} \pm SEM$	$\Delta_{PS} \pm SEM$	$\Delta_{SASA} \pm SEM$	$\Delta G_{bind} \pm SEM$
	(kJ/mol)				
SARS-CoV-2+ Dexamethasone;	-101.047±0.412	-39.769±0.736	73.525±0.468	-11.739±0.039	-79.032±0.673
SARS-CoV-2+ Umifenovir;	-59.769±1.683	-21.553±1.202	34.968±1.705	-7.862±0.221	-54.297±2.013

**Table 2.**  $\Delta G_{bind}$  of Dexamethasone and Umifenovir drugs with the SARS-CoV-2 protein calculated by the MM/PBSA method. Data are shown as mean  $\pm$  standard error of mean (SEM).  $\Delta_{vdW}$  = van der Waal energy,  $\Delta_{Elect}$ =Electrostatic energy,  $\Delta_{PS}$  = Polar solvation energy ,  $\Delta_{SASA}$ = Solvant Accessible Surface Area and  $\Delta G_{bind}$  = Binding energy data of system in kJ/mol calculated by MM-PBSA

### 3.3. Interactions present in SARS-CoV-2+Dexamethasone/Umifenovir:

If the computed free energy is positive, bonded interactions > non-bonded terms. If the computed free energy is negative, non-bonded interactions > bonded terms. For the present case, Gibbs free energy is negative indicating the dominance of favorable non-bonded interactions over unfavorable bonded interactions. The supremacy of non-bonded interactions stabilize the three-dimensional structure of protein-ligand complex and consists of electrostatic,  $\pi$ -effects, van der Waals forces, H-bonds, hydrophobic effects. In these circumstances, we restrict to the non-bonded interactions [38-41] between SARS-CoV-2+Dexamethasone/Umifenovir only. Certain non-bonded interactions between the protein and drugs are shown (at 10ns) in **figures 1 & 2** [42,43].

**--FIGURES 1 & 2--**

#### **4. Conclusion:**

This study proposes a potential approach to the use of Dexamethasone/Umifenovir, to tackle the current pandemic SARS-CoV-2. The MD simulation studies revealed that the RMSD/Radius of Gyration of the (SARS-CoV-2+Dexamethasone), (SARS-CoV-2+Umifenovir) systems reached equilibrium and binding site remained compact/rigid during the simulation. According to  $\Delta G_{\text{bind}}$  bind prediction, the vulnerability against the SARS-CoV-2 with Dexamethasone and Umifenovir are  $(-79.032 \pm 0.673)$  and  $(-54.297 \pm 2.013)$   $\text{kJ} \cdot \text{mol}^{-1}$  respectively. This statistics indicates that that the strength of binding energy of Dexamethasone is 1.5 times stronger than Umifenovir over SARS-Cov-2. Thus this study opens the door toward the use of Umifenovir/Dexamethasone to prevent and treat SARS-CoV-2 infection in humans. Further, in this work, the binding pattern and susceptibility of the inhibitors Dexamethasone/Umifenovir in complex with the SARS-CoV-2 were fully revealed by MD simulations with Gromacs using OPLS-AA force field in conjunction with binding free energy estimation based on the MM/PBSA calculations. Further, this study at the atomic level could also be helpful for design or development of more specific inhibitors in treating human SARS-CoV-2 infection.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

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# Figures

## Fig(1). (SARS-CoV-2+ Dexamethasone) interactions

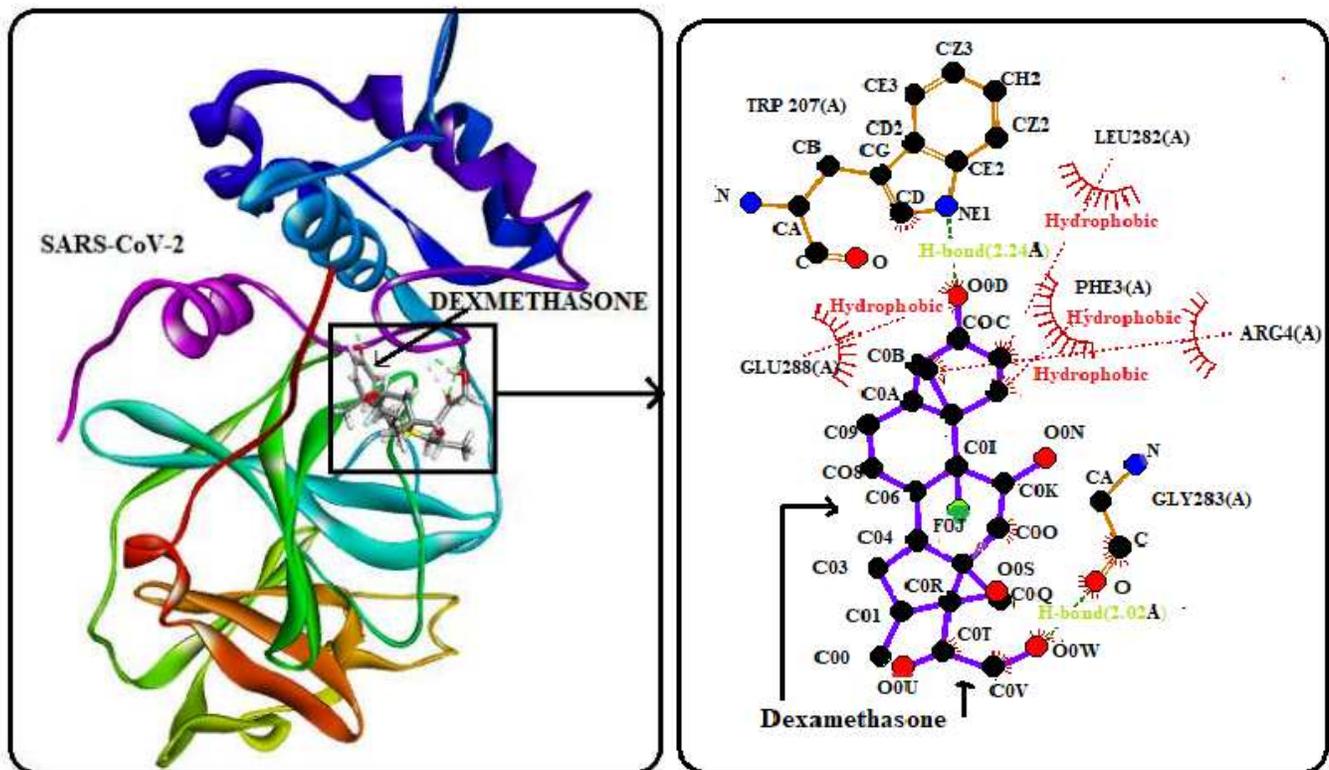


Figure 1

(SARS-CoV-2+ Dexamethasone) interactions

## Fig(2). (SARS-CoV-2 + Umifenovir) interactions

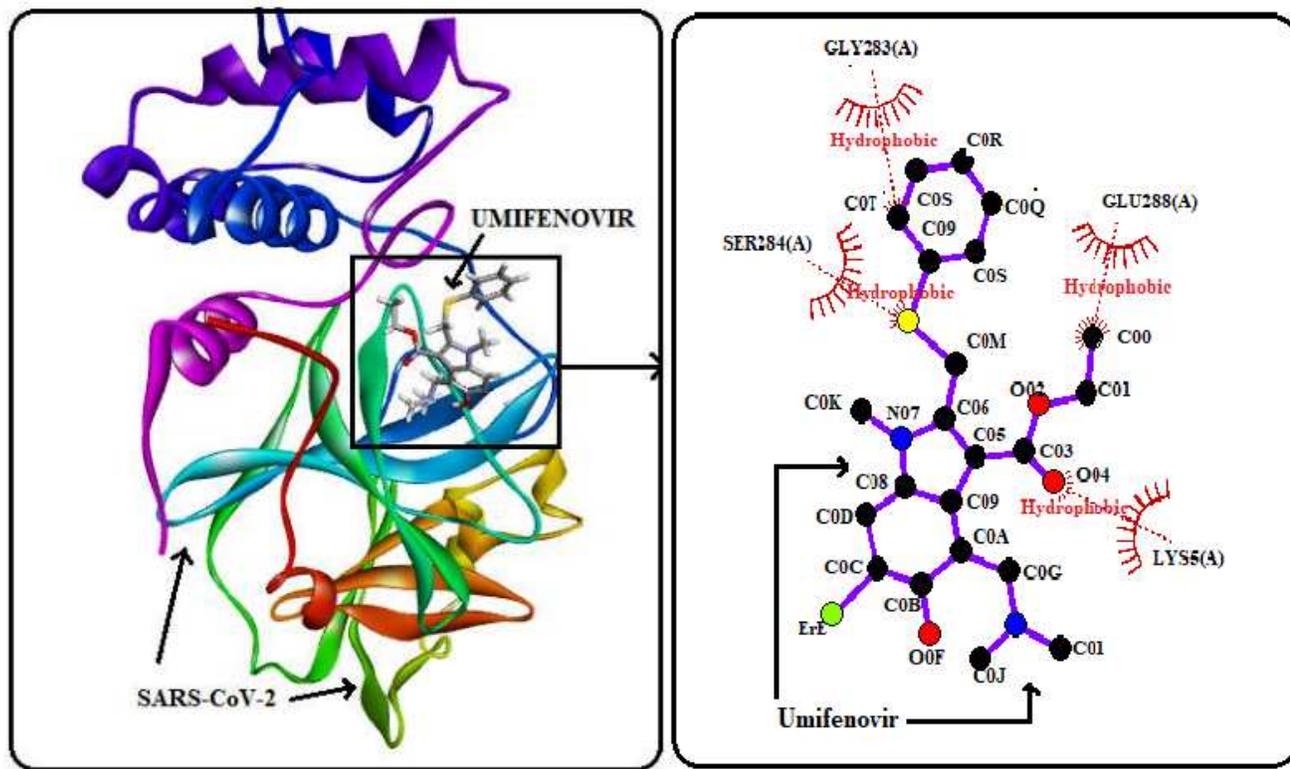


Figure 2

(SARS-CoV-2 + Umifenovir) interactions

## Supplementary Files

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