

Promising Acyclovir and its derivatives to inhibit the protease of SARS-CoV-2: Molecular Docking and Molecular Dynamics simulations

Durgesh Kumar

Atma Ram Sanatan Dharma College, University of Delhi

Kamlesh Kumari

Deen Dayal Upadhyaya College, University of Delhi

Indra Bahadur

Department of Chemistry, Faculty of Natural and Agricultural Sciences, North-West University, South Africa

Prashant Singh (✉ psingh@arsd.du.ac.in)

Atma Ram Sanatan Dharma College, University of Delhi

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Abstract

Till date, more than 40 million people are affected throughout the world due to the COVID-19. Therefore, there is an urgency to find a solution to cure this infection. It is due to the SARS-CoV-2 infection and the authors have targetted the protease of the SARS-CoV-2 so the infection will not spread. Herein, the authors have selected the antiviral drug, acyclovir for the inhibition of protease of the SARS-CoV-2. Acyclovir is a popular and selective antiherpes agent and started a new beginning for the viral infection. The other name of acyclovir is aciclovir and is being used in the treatment of chickenpox, and shingles. Further, it can be used in avoidance of cytomegalovirus infections. Even, acyclovir can used to cure the patients suffering from cold scores, shingles and also decreases the pain.

In the present work, acyclovir (**CMPD1**) and its two derivatives, the first derivative is Ganciclovir (**CMPD2**) and the second derivative is (**CMPD3**). These three molecules were used to inhibit the protease of SARS-CoV-2. It was studied through the molecular docking, molecular dynamics simulations etc. Herein, simulations method were used to calculate relative change in binding free energy under the influence of Amber force field through MM-GBSA. The structural behavior of complex system with acyclovir and its derivatives were observed in term of RMSD and RMSF for all residues. Authors observed that complex of **CMPD3** with the protease is stable and has less fluctuation than the native protease. Further, **CMPD3** follow the creteria of all drug likeness term and it showed good activity against SARS-CoV-2. It was suggested that **CMPD3** may be used as a inhibitor for coronavirus activity to protect life of human being in world.

Introduction

Coronavirus disease (COVID-19) is an infectious disease due to SARS-Cov-2 and it causes more than 40 million infection throughout the world.(Ai et al., 2020; Thomas-Ruddel et al., 2020) The very first case of infection due to SARS-CoV-2 was found in China in year of 2019.(Ahmed, Quadeer, & McKay, 2020) In the begining, several hundreds of people were found suffering from Pneumonia, working in market of sea food & live animals in the Wuhan, city of China. Afterthen, it got spread throught the city and then in most of the countries of the world. The word Coronavirus is based on the latin word CORONA and it means crown.(Lai, Shih, Ko, Tang, & Hsueh, 2020; Sohrabi et al., 2020) This virus consists of core of the genetic material and it is surrounded by proteins spikes, which gives it a look of the crown. The coronavirus is of several types and the initially it is SARS-CoV (severe acute respiratory syndrome).(Bernard Stoecklin et al., 2020) The first case of the infection due to this virus was seen in the 2003 and transmitted through civet cats. Later, MERS-CoV (middle east respiratory syndrome) came into picture and found in the Saudi Arabia in the year of 2012 and many deaths were reported.(Abbad et al., 2019) It is transmitted through camel. But the novel coronavirus occured in 2019 which is found to be transmitted through bats. There are lot of symptoms due to the infection are swelling, breathing problem, cold, fever etc.(Bernheim et al., 2020; Peeri et al., 2020) These problems may be mild to severe and causes respiratory problems in the infected patients. This infection spreads through human to human and surface to human.(Li, Bai, & Hashikawa, 2020) Acyclovir is a popular and selective antiherpes agent and started a new beginning for

the viral infection. ("Acyclovir," 2012; Chavez-Iniguez et al., 2018; Gayretli Aydin et al., 2019; Gonzalez & Rojas, 2018) It is a derivative of the guanosine and it has a problem of its high Log P values that its lipophilicity is high or less soluble in water. Therefore, it decreases its bioavailability. The other name of acyclovir is Aciclovir (ACV) and is being used in the treatment of chickenpox, and shingles. (Abdelhameed, Bakheit, Almutairi, AlRabiah, & Kadi, 2017; Benedetti et al., 2018) Further, it can be used in avoidance of cytomegalovirus infections. Even, acyclovir can be used to cure the patients suffering from cold sores, shingles and also decreases the pain. (Ozdemir & Gokturk, 2019)

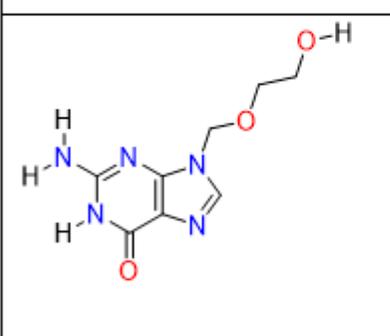
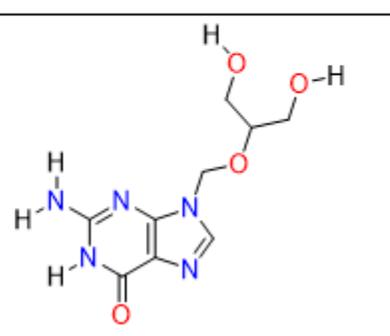
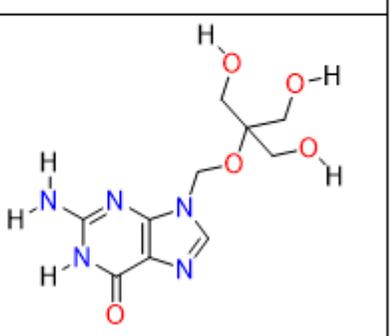
This work deals with the development of potential drug to fight against SARS-CoV-2 against the COVID-19. Lots of research is going on throughout the world for the development of potential drug. In the present work, acyclovir (1), ganciclovir (2) and the designed derivative of acyclovir (3) were chosen for the inhibition of protease of SARS-CoV-2 using computational tools. For the study, pdb file for the protease of SARS-CoV-2 for COVID-19 has been taken from the RCSB and it is complex with N3 ligand with ID of 6LU7. Initially docking was performed using ParDOCK to determine the binding affinity of CMPD 1, 2 and 3 against the protease of SARS-CoV-2 for COVID-19. **CMPD3** showed the binding energy of -4.34 kcal/mol and found to be better than the **CMPD1** (acyclovir) and **CMPD2** (ganciclovir). The bioactivity score and "Lipinski's Rule of Five" were applied on CMPD 1, 2 & 3 using SwissADME and Molinspiration. Further, validation of binding affinity from the docking was studied by molecular dynamics (MD) simulations with MM-GBSA. This study provides detailed information in drug development to combat the viral infection by protease of SARS-CoV-2.

Methodology

Designing of the compound

Based on the literature, acyclovir (1), a popular and selective antiherpes agent is taken and then two compounds were designed using the acyclovir. ("Acyclovir," 2006) The first derivative is known as ganciclovir (2), a potential antiviral drug. The second derivative is a new one (3) using chemdraw. (Kumar, Singh et al., 2019) The synthesis of CMPD1 and CMPD2 can be synthesized using the scheme 1 while for the CMPD3 is expected that it can be synthesized based on scheme 1. (Lazrek et al., 2008) Structures of **CMPD1**, **CMPD2** and **CMPD3** is given in **Table 1**.

Table 1 Structures of the compounds 1,2 and 3 to be used for the inhibition of the protease of SARS-CoV-2 against COVID-19

Acyclovir, CMPD1	Ganciclovir, CMPD2	New derivative, CMPD3
		

Computational Method

The structure of the protease of SARS-CoV-2 complexed with N3 is taken from RCSB, protein data bank and then was prepared using Pymol and Chimera. Further, the compounds 1, 2 and 3 were optimized before the study using the gaussian.(Goodsell et al., 2019; Kumar, Kumari, Jayaraj, & Singh, 2019) Then, docking was performed between the above mentioned compounds (1, 2 & 3) and the protease of protease of SARS-CoV-2. The binding affinity of these complexes was predicted based on the equation given below.(Gupta, Gandhimathi, Sharma, & Jayaram, 2007)

$$E = \sum E_{el} + E_{vdW} + E_{hpb}$$

Further, the biological score of these molecules was determined using SwissADME and Molinspiration, the web servers.(Ibrahim, Uzairu, Shallangwa, & Uba, 2020; Lohidashan, Rajan, Ganesh, Paul, & Jerin, 2018) It describe the pharmacokinetics of the drugs or molecules in the body based on the the absorption, distribution, metabolism and excretion (ADME). Lipinski's Rule of Five states that drug should not violate more than one activity.(Kalirajan, Pandiselvi, Gowramma, & Balachandran, 2019) It describe to be a potential drug for good oral bioavailability should follow some parameters like hydrogen bond donor <5, hydrogen bond acceptor <10, molecular mass < 500, octanol-water partition coefficient (log *P*) and TPSA <140 Å².

Further, molecular dynamics (MD) simulations were performed for the protease of SARS-CoV-2 with or without the **CMPD1**, **CMPD2** and **CMPD3** for a time of 10 ns. Different

trajectories like root mean square deviation (RMSD), root mean square fluctuation (RMSF) and number of hydrogen bonds were determined through MD simulations. (Duan et al., 2019; Skjevik et al., 2015; Srivastava & Sastry, 2012; Wang et al., 2019; Xu, Sun, Li, Wang, & Hou, 2013)

The RMSD curve is obtained from correlating time with the deviations to understand the stability of the complexes in comparison of the protease alone and can be determined based on the following equation. (Alexandrescu, Snyder, & Abildgaard, 2001; Bruschiweiler, 2003)

$$RMSD = \sqrt{\frac{1}{N} \sum_{i=1}^N (X_i^m - X_i^1)^2 + (Y_i^m - Y_i^1)^2 + (Z_i^m - Z_i^1)^2}$$

Where N is the number of atoms, X^m , Y^m , Z^m are the Cartesian coordinates of the initial structure and X^1 , Y^1 , Z^1 are the Cartesian coordinates of trajectory at frame t.

RMSF is used to understand the structural flexibility and obtained by plotting number of residue with fluctuations and calculated based on the equation given below. (Assadollahi, Rashidieh, Alasvand, Abdolahi, & Lopez, 2019; Hechemy, 1987)

$$RMSF = \sqrt{\frac{1}{T} \sum_{i=1}^T (X_i - \bar{X})^2}$$

Where T is the number of trajectory frames and \bar{x} is the time-averaged position.

Further, MD simulations were used to calculate the relative change in energy for the formation of complexes and AMBER18, utilizing the ff14SB force field was chosen. (Cinaroglu & Timucin, 2019) Additionally, the parameters of compounds 1, 2 and 3 for molecular dynamics simulation were generated using antechamber module of AMBER suite utilizing Generalized Amber Force Field (GAFF). Different trajectories were drawn using the CPPTRAJ modules. (Mukherjee, Patra, Barua, & Jayaram, 2011; Roe & Cheatham, 2013) Using the trajectories obtained from the MD simulation, change in enthalpy for the formation of the complex is calculated based on the equations given below. (Al-Anazi, Al-Najjar, & Khairuddean, 2018; Du et al., 2011; Greenidge, Kramer, Mozziconacci, & Sherman, 2014; Mena-Ulecia, Tiznado, & Caballero, 2015)

$$\Delta H = \Delta E_{MM} + \Delta G_{solv}$$

$$\Delta E_{MM} = \Delta E_{internal} + \Delta E_{elec} + \Delta E_{vdw}$$

$$\Delta G_{solv} = \Delta G_{GB} + \Delta G_{SA}$$

ΔH - Change in enthalpy;

ΔE_{MM} - change of the MM energy in the gas phase;

$\Delta E_{internal}$ & ΔE_{elec} - electrostatic energy;

ΔE_{vdw} - van der Waals energy;

ΔG_{solv} - solvation free energy;

ΔG_{GB} - Energy from polar contribution;

ΔG_{SA} - Energy from non-polar part

Results And Discussion

Docking

In docking study, prepared target protein and compounds were loaded into ParDOCK, a web server. The binding energy for the formation of the complex with the protease of SARS-CoV-2 was calculated and given in **Table 2**. The docked poses along with the types of interaction with different amino-acids is given in **Table 2**. Based on the results obtained, it is cleared that CMPD3 binds effectively with the protease of SARS-CoV-2 with a binding energy of -4.34 kcal/mol, in comparison of CMPD2 and CMPD3 having energy of -3.92 and -3.74 kcal/mol respectively.

[Please see the supplementary files section to view Table 2.]

Bioactive score

Based on the Lipinski's Rule of Five for the compounds 1, 2 and 3, all of them have sparingly to highly soluble. Further, the SwissADME, web-server was used to calculate physicochemical, pharmacokinetic, drug like and other related parameters for the

compounds as in **Table 3**. Moreover, for drug development targeting oral administration, the solubility is one of the key properties in the influencing of drug absorption. Thus, poorly soluble drug in water to deliver an enough quantity of active ingredient into target site in the pharmaceutical dosage. It was observed that these molecules follow all the parameters of drug likeness score.

Table 3 Physicochemical, pharmacokinetic, drug like and other related parameters of the compounds **1, 2** and **3**

Properties	Acyclovir, CMPD1	Ganciclovir, CMPD2	CMPD3
Log S (ESOL)	-0.41 very soluble	-0.42 very soluble	0.37 highly soluble
Heavy atoms	16	18	20
MW (g/mol)	225.20	255.23	285.26
No. of rotational bonds	4	5	9
No. H-bond acceptors	5	6	7
Num. H-bond donors	3	4	5
Log P _{o/w} (iLOGP)	0.48	0.16	-0.58
GPCR ligand	-0.03	0.28	0.21
Lipinski's Rule of Five	Yes, 0 violation	Yes, 0 violation	Yes, 0 violation
Log K _p (skin permeation) cm/s	-8.78	-9.04	-10.20
TPSA(Å ²)	119.05	139.28	159.51
Bioavailability Score	0.55	0.55	0.55
Synthetic accessibility	2.47	2.61	2.74
Ion channel modulator	-0.09	-0.10	-0.04
Kinase inhibitor	0.30	0.43	0.46
Nuclear receptor ligand	-1.47	-1.15	-0.94
Protease inhibitor	-0.80	-0.54	-0.38
Enzyme inhibitor	0.91	1.03	0.80
Volume	187.75	212.60	237.10

Molecular dynamics (MD) simulations

MD simulations of complex between the protease of SARS-CoV-2 with the **CMPD1**, **CMPD2** and **CMPD3** respectively were effectively run for 10 ns time scale.

In order to understand the stability of the protease of SARS-CoV-2 with and without the **CMPD1**, **CMPD2** and **CMPD3**, trajectories of RMSD, RMSF and hydrogen bonding plot were studied.

RMSD was used to study the stability of the protease in complexed with the **CMPD1**, **CMPD2** and **CMPD3**. Herein, RMSD values of the backbone atoms of the protease of SARS-CoV-2 to the complex structure through the simulations with time as a function given in **Figure 1**. The native protease has high RMSD in comparison of the complexed form with the compounds 1, 2 and 3. The complex formed are highly stable as the RMSD of the complex is less than 2 Å. Further, the RMSF was used to study the fluctuation in the protease with or without compounds.

Further, stability of the complexes of protease of SARS-Cov-2 with the compounds 1, 2 and 3 were studied through the hydrogen bonding as in Figure 3, 4 and 5. Based on the plots, the maximum number of bonds are observed in complex with **CMPD3**, indicates more stability of the complex.

The change in enthalpy for the formation of the complexes of protease of SARS-Cov-2 with the compounds 1, 2 and 3 was determined using MD simulation and plots are given in **Figure 6**. Further, the change in enthalpy was calculated as in **Table 4**. Formation of the complex with the **CMPD3** gave the minimum change in enthalpy of -19.9099kcal/mol. It shows the maximum stability to the protease of SARS-CoV-2.

Table 4 Enthalpy for the formation of complex of protease of SARS-CoV-2 with CMPD1, 2 and 3 for MD simulation of 10 ns

Energy component	Average value of protease of SARS-CoV-2 with CMPD1, 2 and 3 at 300K		
	d-t-dt complex using CMPD1	d-t-dt complex using CMPD2	d-t-dt complex using CMPD3
VDWAALS	-23.7730	-29.4629	-26.8133
EEL	-37.5497	-15.6378	-26.5898
EGB	46.1555	31.8804	36.7038
ESURF	-2.6023	-3.8024	-3.2106
ΔG_{gas}	-61.3227	-45.1008	-53.4031
ΔG_{solv}	43.5532	28.0779	33.4932
ΔH	-17.7695	-17.0228	-19.9099
d- compound; t- complex of protease of SARS-CoV-2; dt- complex of protease of SARS-CoV-2 with compound			

Conclusion

Acyclovir and its derivatives were taken as the acyclovir is an antiviral drug. Interaction of the **CMPD1** (acyclovir); **CMPD2** (ganciclovir) and **CMPD3** (new compound) against the protease of SARS-CoV-2 were studied using the computational tools, molecular docking and molecular dynamics simulations. Based on the results obtained CMPD3 is a promising candidate for the inhibition of protease of SARS-CoV-2 at 300K.

Conflict Of Interest

The authors declare no conflict of interest.

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Figures

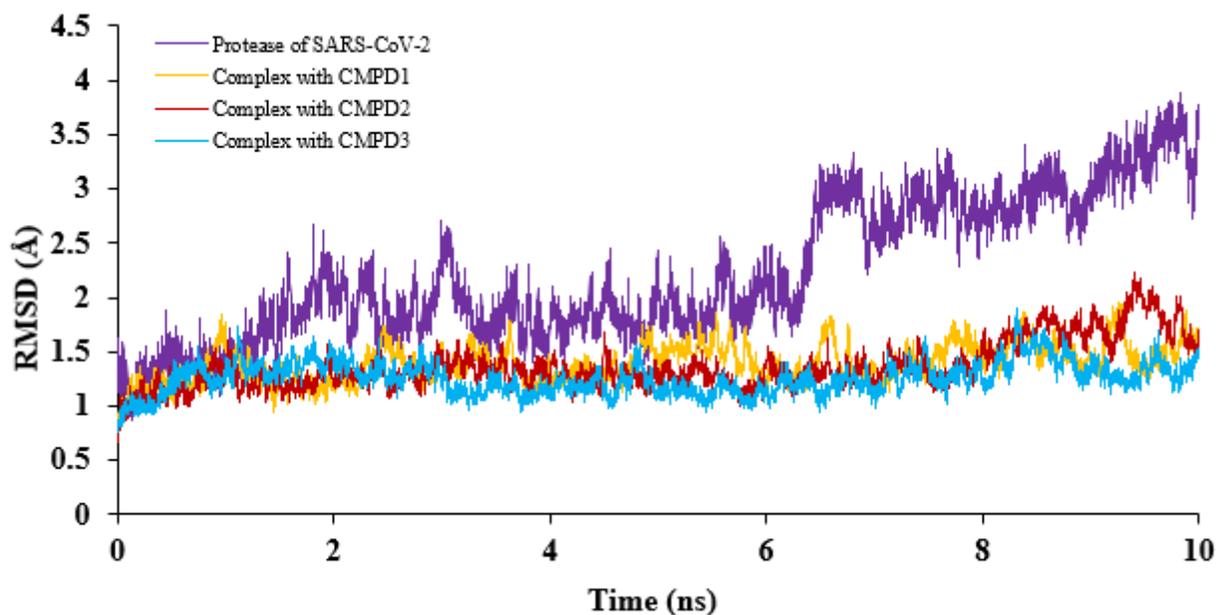


Figure 1

RMSD plot protease of SARS-CoV-2 with or without compounds 1, 2 and 3 The RMSF plots of protease of SARS-CoV-2 showed huge fluctuation but after the formation of complex the fluctuation decreases as in Figure 2. Minimum fluctuations are observed in the case of complex between the protease of SARS-CoV-2 with the CMPD3.

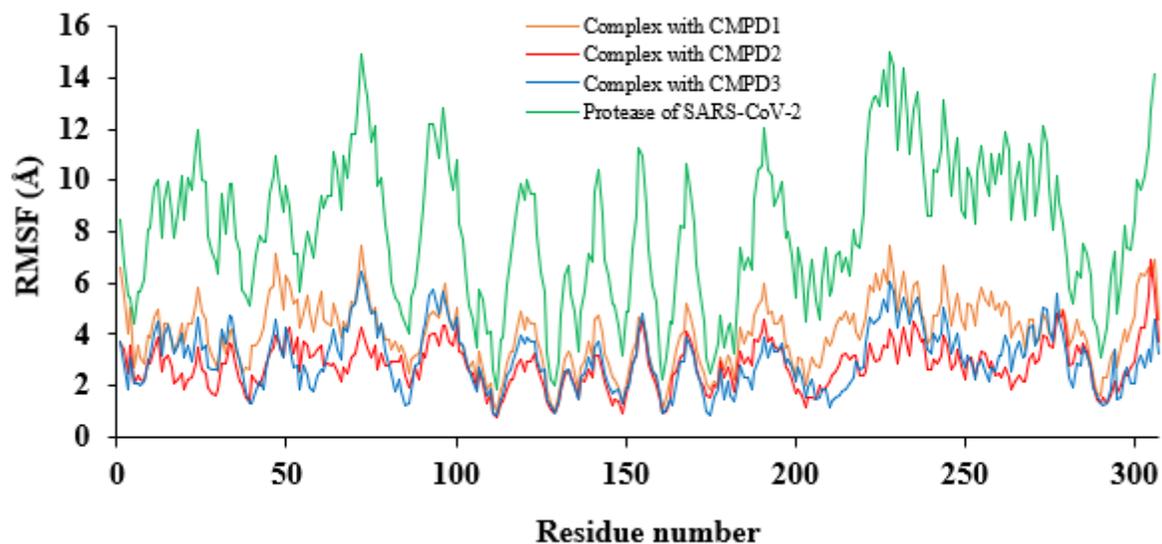


Figure 2

RMSF plot protease of SARS-CoV-2 with or without compounds 1, 2 and 3

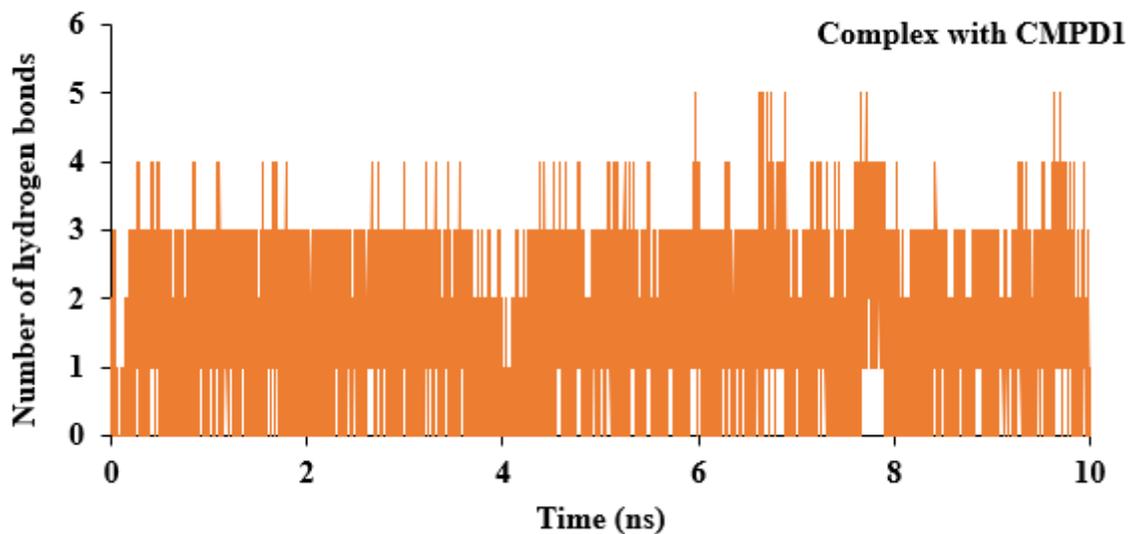


Figure 3

Hydrogen bonding for the formation of complex with CMPD1

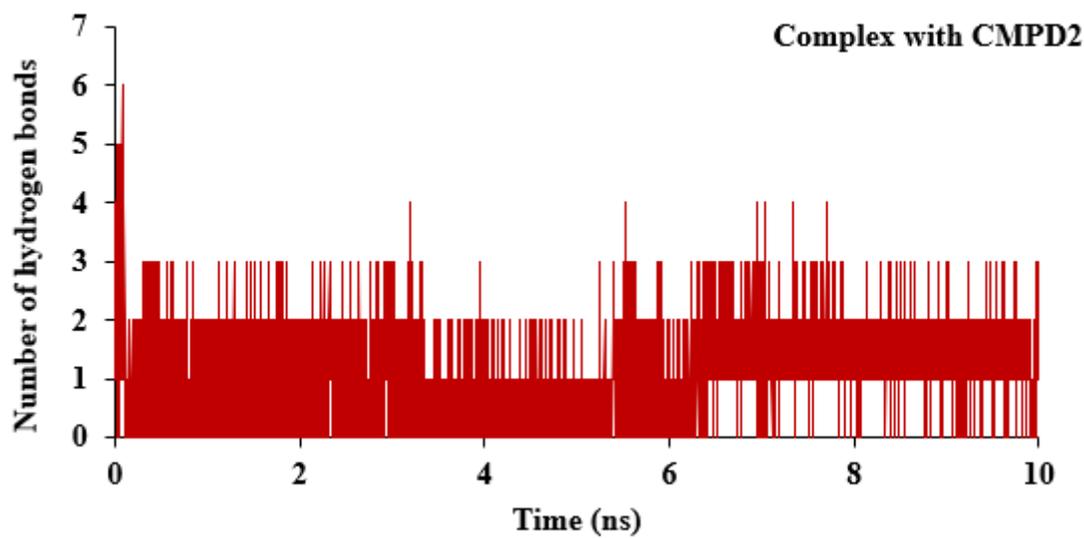


Figure 4

Hydrogen bonding for the formation of complex with CMPD2

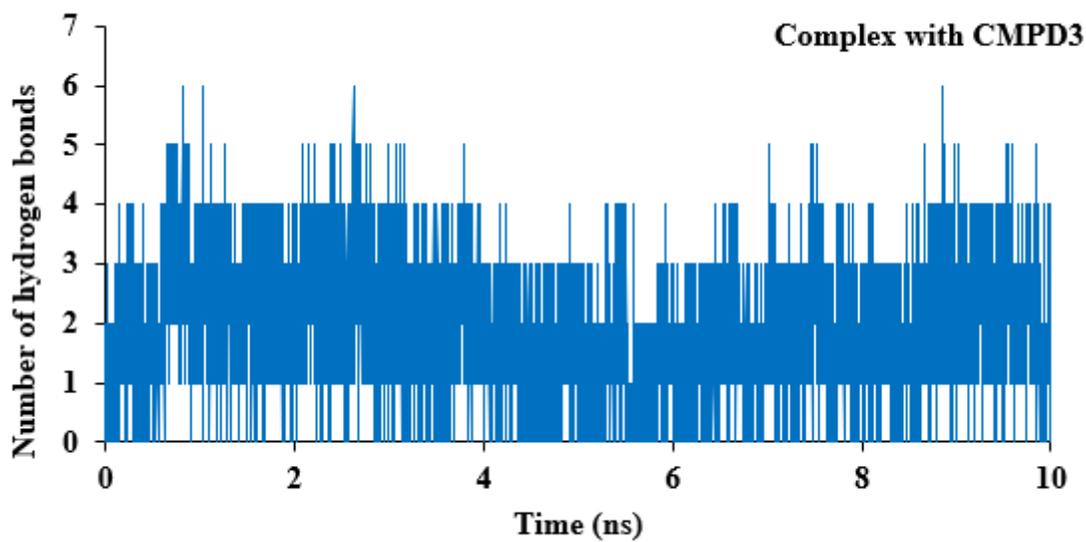


Figure 5

Hydrogen bonding for the formation of complex with CMPD3

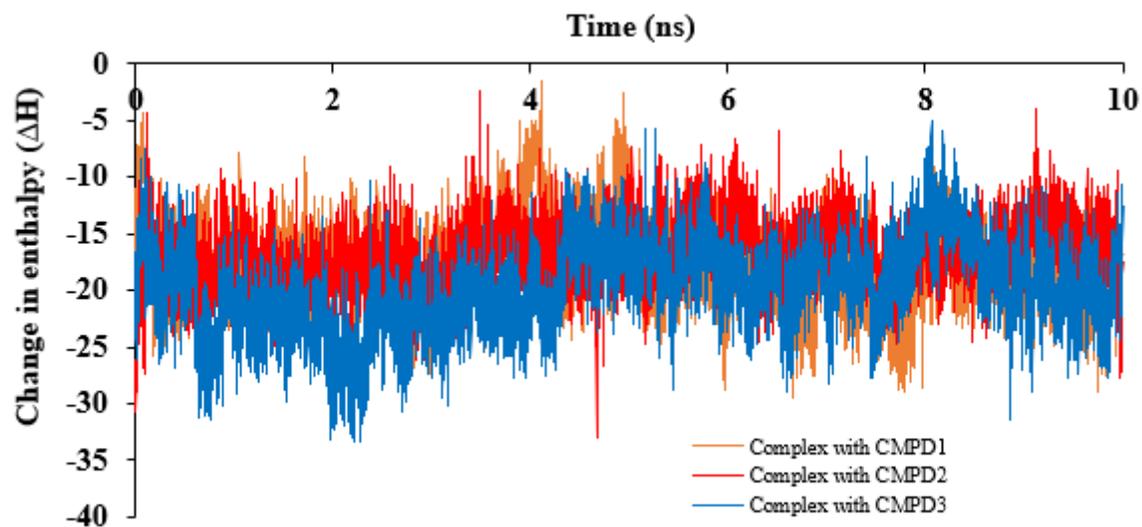


Figure 6

Enthalpy for the formation of complex of protease of SARS-CoV-2 with CMPD1, 2 and 3 for MD simulation of 10 ns

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [graphicalabstract.PNG](#)
- [Scheme1.PNG](#)
- [table2.docx](#)