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Potential Docking Affinity of Three Approved Drugs Against SARS-CoV-2 for COVID-19 Treatment

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Abstract

Objectives: As the COVID-19 is rapidly spreading entire world and even though vaccines are distributing on emergency basis. There are enormous delays in supply chain due to huge gap between demand and production and also time factor for different phases of vaccination in the entire world. There is urgent need of alternate effective drug candidates from among the drugs already approved by FDA.

Methods: We have studied the virtual interaction of crystal data structures of protein downloaded from protein data bank (PDB ID 7BRP) docked with corticosteroid drug candidates approved by FDA for other medical purposes which have less side effects. The results are analyzed in contrast some drugs candidates currently using for the treatment of COVID-19.

Results: The binding energies in kilocalories/mole obtained from the docking of 7BRP protease with ligands under investigation Betamethasone Phosphate (-6.9), Fluticasone (-6.1) and Dexamethasone (-5.9) and also with currently using drug candidates Remdesivir (-6.5), Lopinavir (-6.0), Baceprivir (-5.7), Rabavirin (-6), Ritinovir (-5.3), Hydroxyquinoline (-5.0), Chloroquine (-4.7), Oseltamivir (-4.6), Favipiravir (-3.9).

Discussion: The docking results suggest a higher binding affinity of the drug molecules under investigation against SARS-CoV-2 in contrast with other drug candidates currently being used for the treatment of COVID-19. We have analyzed bond interactions of protein-ligand from images in 10 modes of investigated drugs in contrast with Remdesivir and discussed the advantages of inhalation methods of drug fluticasone.

Conclusion: From this study, it can be suggested that these carticosteroid drugs are promising candidates for antiviral treatment with high potential to fight against SARS-CoV-2 strain which needs further clinical studies. Especially, fluticasone an inhaler drug promising candidate which targets the infected lungs by COVID-19.

Keywords: COVID-19 • FDA approved drugs • Docking • SARS-CoV-2 protease • Treatment methods

Introduction

As on today February 3rd 2021 there are around 2.24 million deaths happened due to COVID-19 pandemic entire world. In silico approach and docking studies has become a promising tool for drug discovery and development. Molecular docking is an in silico approach to identify virtual interaction between protein and ligand molecules with low energy conformation [1]. It involves identification of hit molecules, optimization of lead compound and virtual screening [2-5]. Anti-malarial drugs like chloroquine and hydroxychloroquine showed prominent interaction with SARS spike glycoprotein-Human ACE2 complex in contrast with oseltamivir, ritonavir, remdesivir, ribavirin and favipiravir which exhibited high affinity with COVID-19 main protease [6]. It is well noticed in the literature about the potentiality of oseltamivir, [7] lopinavir, [8] ritonavir, [8] remdesivir, [9] favipiravir, [10] ribavirin, [10] chloroquine and hydroxychloroquine [11] as antiviral agents. Majority of the drugs are HIV protease inhibitors [12]. We have studied virtual interaction and docking with COVID-19 main protease downloaded from protein data bank (PDB ID 7BRP). Some of the Potential Therapeutic Target Against SARS-CoV and SARS-CoV-2 Several similarities between SARS-CoV-2 and SARS-CoV have been reported. After the sequencing of SARS-CoV-2 has been done [13], there are several similar factors reported between SARS-CoV-2 and SARS-CoV. Several number of molecular modeling experiments lead to find the potential candidate against novel coronavirus SARS-CoV-2. Phylogenetic analysis. Lu, et al. [13,14] shown the SARSCoV-2 originated from bat revealed similarity between the 3D structures of SARS-CoV-2 and SARSCoV in the RBD, which has shown the pathway in identifying and developing potential target against SARSCoV-2. Several antiretroviral drugs reported to show effectiveness against COVID-19 including ritonavir, [15,16] lopinavir, [16] alone or in combination with oseltamivir, [16] remdesivir, chloroquine and hydroxychloroquine [17]. Among them ritonavir, remdesivir, chloroquine and hydroxychloroquine has shown efficacy at cellular level [15]. In silico methods are very useful for screening of candidates from drug libraries. [18,19]. Our current studies reveal identification of potential therapeutic already approved drug candidates, mainly focused on corticosteroids against COVID-19 using virtual interactions and docking studies.

Materials and Methods

We used Auto Dock Vina extended on 1Å Samson 2020 (software for adaptive modeling and simulation of nano systems) [20]. We performed blind dockings (blind docking refers to the use of a grid box which is large enough to encompass any possible ligand-receptor complex). Protein structures are downloaded from protein data bank. All the conformational ligand structures

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were created by using smiles codes on Samson software to have the most stable structure using energy minimization for the force field and conjugate gradient method. The ligand and protein molecules were converted to their proper file format pdb files using Discovery Studio Visualizer 2020. The docking was done using an exhaustiveness value of 8 with a measurement of 10 modes each docking. All other parameters of software were kept as default and all bonds contained in ligands could rotate freely, considering the receptor as rigid. The final visualization of the docked structure was performed using Discovery Studio Visualizer 2020. The results obtained from these experiments indicated the strong interactions of the potential drug candidates against COVID-19 main protease.

Comparison of Binding affinities

After successful docking of these drugs into the COVID-19 main protease in complex, the results show various modes of drug-protein interactions are generated with docking score (binding energy). The structures of ligand molecules used for docking are shown in the Figure 1. The binding mode with least binding energy is regarded as the best mode of binding as it is most stable for the ligand. The binding energies of drug candidates under investigation in contrast currently used drugs for treatment purposes of COIVD-19 are summarized as Table 1 and shown in the graph in Figure 2. From the binding energies in different modes, betamethasone phosphate has shown more bonding affinity with protein when compared to remedesivir and lopinavir. Other two drugs Fluticasone and Dexamethasone have also shown closer binding affinity to remedesivir but comparatively also closer to lopinavir and ribavirin and more binding affinity than other drugs under investigation.

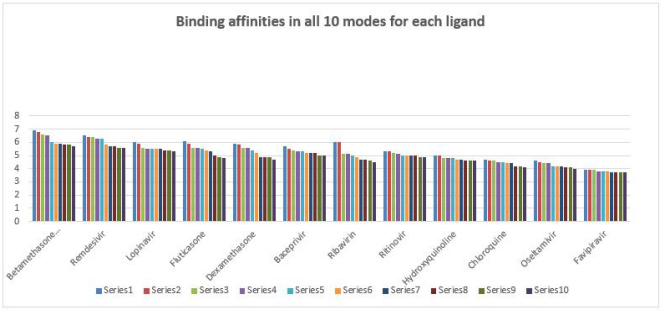

Figure 1. Binding affinity graph of all ligands in all 10 modes for each ligand (Positive values are taken for graphical comparison purpose).

Comparison of protein-ligand binding interactions with graphs

The protein-ligand binding interactions are studied for selected comparable drug candidates like betamethasone phosphate, fluticasone, dexamethasone with remedesivir. It is also revealed the interaction of specific amino acids that take part in the drug-protein interactions. All the docked structures were visualized by Discovery Studio Visualizer 2020. The visualized 3D pictures of sitting of ligand in protein structure and 2D pictures of bonding interactions are shown for all the selected four drug candidates betamethasone phosphate, fluticasone, dexamethasone, remedesivir in Figures 3-6 respectively. The number and types of bonds formed in different modes of bonding interaction in 2D pictures are summarized in Figure 7.

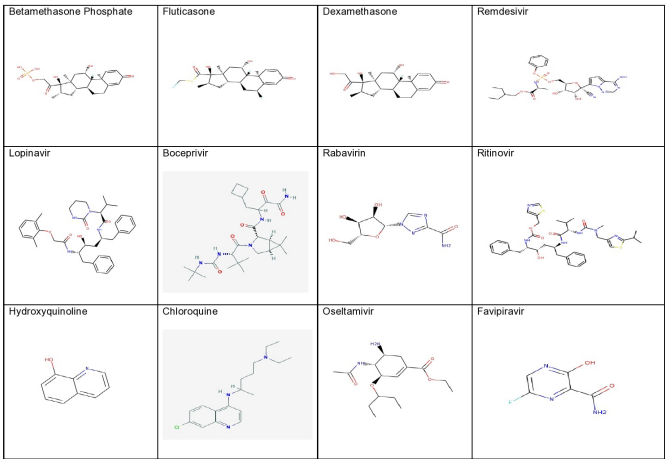

Figure 2. Chemical Structures of molecules docked with main protease of SARS-CoV-2 from protein data bank (PDB ID 7BRP).

Table 1. Binding affinity of ligands in all 10 modes in kilocalories mole $^{-1}$.

Modes	Betamethasone phosphate	Remdesivir	Lopinavir	Fluticasone	Dexamethasone	Baceprivir	Ribavirin	Ritinovir	Hydroxyquinoline	Chloroquine	Oseltamivir	Favipiravir
1	-6.9	-6.5	-6	-6.1	-5.9	-5.7	-6	-5.3	-5	-4.7	-4.6	-3.9
2	-6.8	-6.4	-5.9	-5.9	-5.8	-5.5	-6	-5.3	-5	-4.6	-4.5	-3.9
3	-6.6	-6.4	-5.6	-5.6	-5.6	-5.4	-5.1	-5.2	-4.8	-4.6	-4.4	-3.9
4	-6.5	-6.3	-5.5	-5.6	-5.6	-5.3	-5.1	-5.1	-4.8	-4.5	-4.4	-3.8
5	-6	-6.3	-5.5	-5.5	-5.4	-5.3	-5	-5	-4.8	-4.5	-4.2	-3.8
6	-5.9	-5.8	-5.5	-5.4	-5.2	-5.2	-4.9	-5	-4.7	-4.4	-4.2	-3.8
7	-5.9	-5.7	-5.5	-5.3	-4.9	-5.2	-4.7	-5	-4.7	-4.4	-4.2	-3.7
8	-5.8	-5.7	-5.4	-5	-4.9	-5.2	-4.7	-5	-4.6	-4.2	-4.1	-3.7
9	-5.8	-5.6	-5.3	-4.9	-4.9	-5	-4.6	-4.9	-4.6	-4.2	-4.1	-3.7
10	-5.7	-5.6	-5.3	-4.8	-4.7	-5	-4.5	-4.9	-4.6	-4.1	-4	-3.7

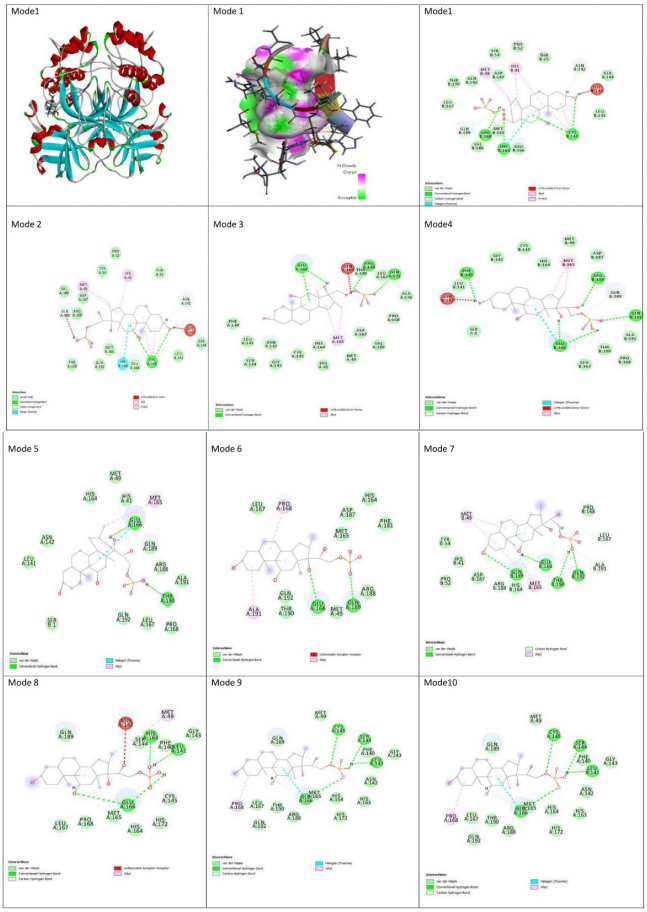

Figure 3. Binding interactions of betamethasone phosphate with protein: All the 10 modes of binding interactions are taken for discussion.

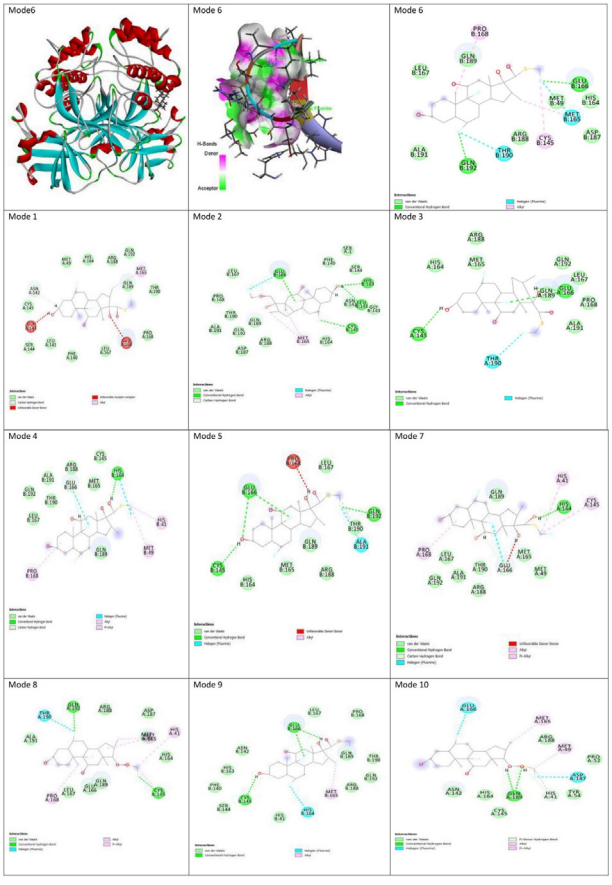

Figure 4. Binding interactions of Fluticasone with Protein: All the 10 modes of binding interactions are taken for detailed discussion.

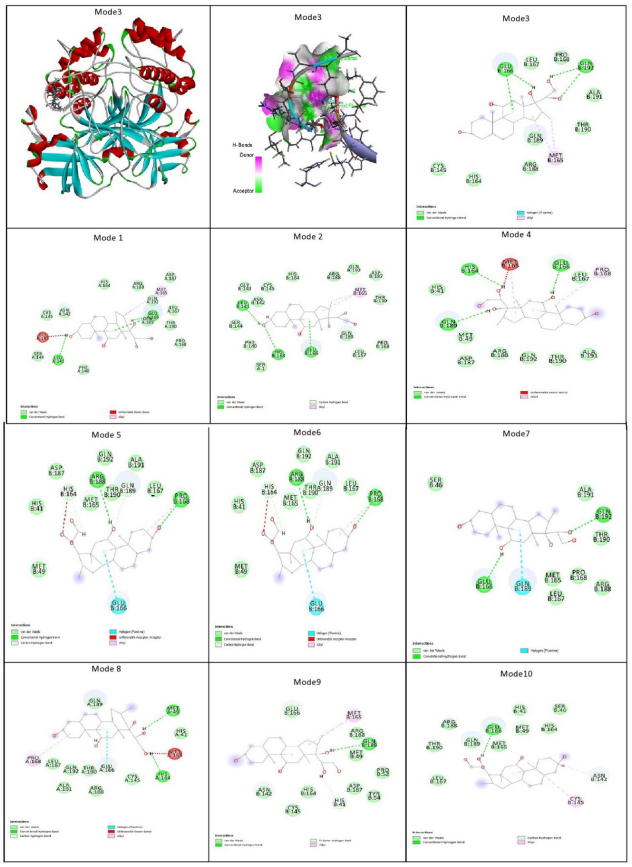

Figure 5. Binding interactions of Dexamethasone with Protein: All the 10 modes of binding interactions are taken for detailed discussion.

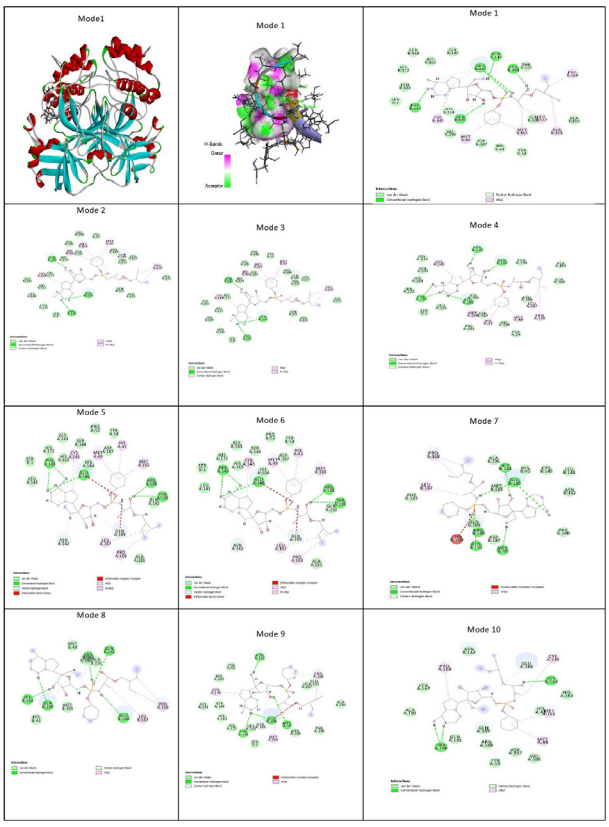

Figure 6. Binding interactions of Remedesivir with Protein: All the 10 modes of binding interactions are taken for detailed discussion.

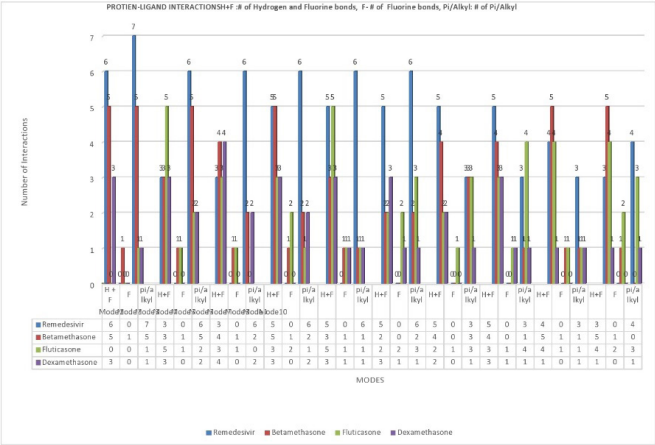

Figure 7. Protein-Ligand interactions in 10 modes and number of different types of bonds formed.

From the binding affinity (Table 1 and Figure 2) and bonding interaction it is clearly understood that betamethasone phosphate has shown more binding affinity than remedesivir and comparatively more stable in all the ten modes as per the binding affinity values. Even though remedesivir has shown a greater number of pi-alkyl, alkyl binding interactions with protein binding sites, the presence of strong F-hydrogen bonding and F-pi bond interactions are predominant in case of betamethasone phosphate, a corticosteroid. The presence of alpha, beta unsaturated keto group in betamethasone phosphate is also responsible for its more binding affinity when compared to remedesivir.

Results and Discussion

The presence of F-hydrogen bonding and F-pi interactions and also the presence of alpha, beta unsaturated ketone in case of other two corticosteroid ligands like Fluticasone and Dexamethasone are responsible for showing binding affinity closer to remedesvir, lopinavir which also show more binding affinity than other drug candidates docked in the study.

Fluticasone is an inhaler drug used in patients with obstructive pulmonary diseases (e.g. asthma or COPD). Fluticasone propionate is an optimized drug for inhalation. Inhaled drugs are the mainstay of treatment in the care of pulmonary diseases such as asthma and COPD [21-23]. Compared with other routes of administration, respiratory drugs that are specifically designed for inhalation. Significant benefits, including direct delivery to the disease target site, rapid onset of action, high and long-term pulmonary efficacy, and reduced risk of systemic side effects [24,25]. It can be readily used by the people moving in more infected areas where the COVID-19 infection is severely spread. It can also be used as preventive treatment upon the doctors advise and it is easy to carry inhaler. It needs further clinical studies to use this as inhaler or intravenous administration for preventive and cure measures of COVID-19.

Conclusion

Based on the above results, it is clear that three drug candidates betamethasone phosphate, fluticasone and dexamethasone approved by FDA for other medical purposes, have high potential bond affinity and binding interactions against SARS-CoV-2 protease on par with the drugs currently using for COVID-19 treatment. Fluticasone is a promising inhaler drug candidate which targets the infected lungs by COVID-19. It needs further clinical studies to suggest them as alternative medical treatments for COVID-19.

Conflicts of Interest

All the authors declare that there is no competing interest in this work.

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