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Research Article

Histone Deacetylase Inhibitors as Potential COVID-19 Virus RNA-Dependent RNA Polymerase Inhibitors: A Molecular Docking and Dynamics Study

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Abstract

The novel coronavirus disease that initially appeared in 2019, commonly identified as COVID-19 is an acute infectious disease precipitated by the SARS-CoV-2 and has become a severe pandemic health crisis. People stricken with a severe case of COVID-19 are subject to a relatively higher mortality rate, which is brought about predominantly by the difficulty of having potent and specific antiviral drugs for its treatment. In this context, the viral RNA-dependent RNA polymerase (RdRp) is an attractive target for antiviral inhibitors, mainly because of its essential role in processing the polyproteins translated from viral RNA. Moreover, histone deacetylases inhibitors represent one of the most promising antiviral agents. Therefore, in this contribution, the *in silico* structure-based drug design approach was employed to identify novel structural characteristics for the potential repurposed activity of HDACIs as antivirals against COVID-19. Herein, 12 HDAC inhibitors were screened to explore their potential anti-viral activity against RNA-dependent RNA polymerase (RdRp) (6NUR). Results revealed that large number of the screened HDAC inhibitors are strongly bound into the active binding site of crystallographic structure of RNA-dependent RNA polymerase (RdRp) (6NUR) with lowest CDOCKER energy and CDOCKER interaction energy are very close to those of the control drug remdesivir. Importantly, the virtually screened HDAC inhibitors, particularly, Givinostat, Pracinostat, Panobinostat, Romidepsin (FK228) and its active metabolite (RedF) could be promising candidates for COVID-19 RNA-dependent RNA polymerase (RdRp) inhibitors. Significantly, these inhibitors should be evaluated on their effectivity when treating COVID-19, specifically using the drugs that have been approved for clinical trials with limited toxicity.

Keywords: COVID-19; HDAC inhibitors; Repurposing strategy; SARS-CoV-2; Molecular docking; dynamics

Introduction

Towards the end of year 2019, an unprecedented global outbreak of a newly identified coronavirus classified as severe acute respiratory syndrome (SARS-CoV-2), precipitated a global pandemic disease named COVID-19 [1–4]. The global health concerns have been elevated in recent times, due to the pandemic of (COVID-19) [5]. The extreme transmission rates and spread of disease have made the search for drug candidates to help in the reduction of this disease a global priority. A very successful strategy to combat a health crisis like this is drug repurposing, or more commonly recognized as repurposing or redirecting methods. Hence, drug redirecting of existing drugs is urgently required and could be a promising strategy for optimizing antiviral therapies that can successfully combat the SARS-CoV-2 infection in a short time. During the last few months, numerous FDA approved drugs and drugs under FDA examination have been repurposed for treating COVID-19 [6,7].

On the other hand, it is apparent that histone deacetylases inhibitors, in addition to their long history of use as targeted potent treatments for cancers [8,9], anti-epileptics, mood stabilizers [10], antiparasitic [11] and anti-inflammatory [12], they have a potential role as novel therapeutic agents against viral infections [13]. The majority of HDAC inhibitors have three common pharmacophore patterns characterized as: A) Cap, B) linker, and C) Zinc Binding Group (ZBG) [14] as shown in Figure 1. Recently, six HDAC inhibitors (Figure 2) have been accepted as anticancer agents namely; Vorinostat (SAHA), [15] Romidepsin (FK228) and its active metabolite RedFK [16]. Belinostat (PXD101) [17], Pracinostat [18], Panobinostat (LBH-589) [19] and Chidamide (CS055) [20].

In addition, many other drugs are currently undergoing clinical trials to treat a diverse range of cancers such as Mocetinostat, Givinostat, Recolinostat, Tacedinaline, and Entinostat (Figure 1) [21–26].

It has been reported that Trichostatin A and valproic acid inhibited the appearance of inherent antiviral particles such as IFNβ, interferon-simulated genes, and other proteins involved in TLR3/TLR4 signaling. Additionally, they blocked microglial and astrocytic cytokine and chemokine gene expression, however, with different effects on other groups of cytokines [27,28]. Furthermore,

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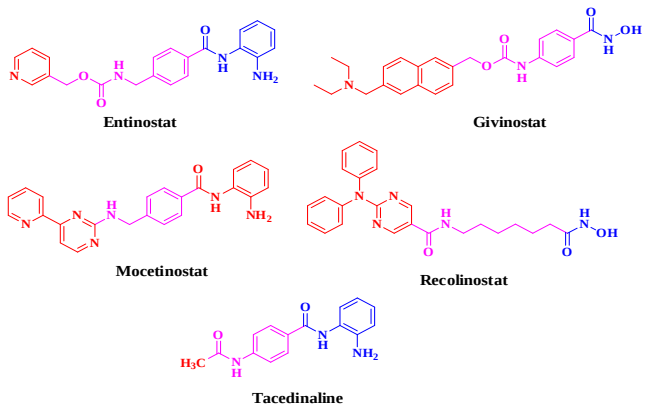

Figure 1: Structure of some anticancer HDACIs in clinical trials.

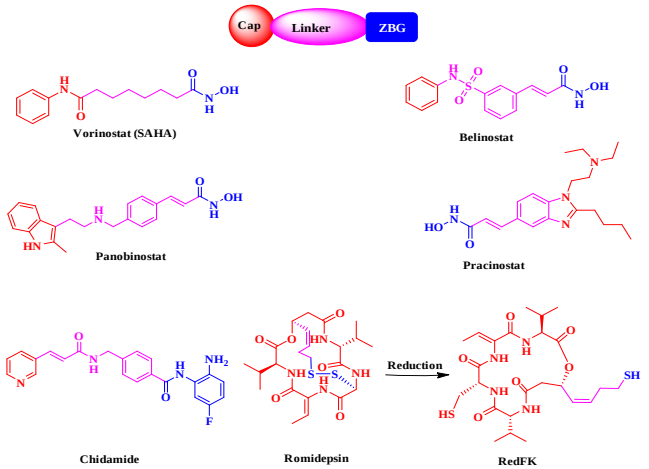

Figure 2: Structure of the approved anticancer HDACIs.

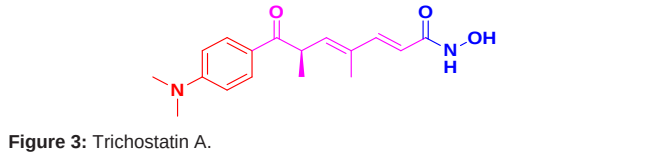

Figure 3: Trichostatin A.

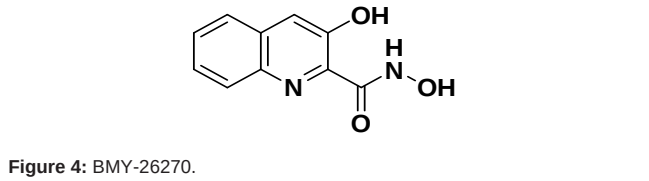

Figure 4: BMY-26270.

TSA reduces the number of viral genomes in Herpes Simplex Virus-1 infected cells [29] (Figure 3).

Notably, in January 2013, after the successful initial round of *in vitro* research, the Danish Aarhus University Hospital was awarded $2 million to Dr. Ole Søgaard by the Danish Research Council, allowing them to proceed with clinical trials on 15 humans [30]. One report observed the use of vorinostat, entinostat, panobinostat, as well as romidepsin, precisely to reactivate latent HIV and mitigate the reservoirs. Vorinostat was stated as the lowest in its effectivity of the HDAC inhibitors within this trial [31]. Additionally, in another finding, it showed that romidepsin produced a higher and more persistent level of cell-associated HIV RNA reactivation than vorinostat in latently infected T-cells *in vitro* and *ex vivo* [32]. Furthermore, the hydroxamic acid derivative (BMY-26270) has been suggested it to be a selective inhibitor of purified influenza A RNA-dependent RNA polymerase (RdRp) through IC50 equal to 40 μM. Also, it can inhibit influenza B in an equal potency; inhibited the *in-vitro* capped RNA-dependent transcription of the influenza B viral polymerase with equal potency [33,34] (Figure 4).

Within the search for potential drug targets, 3CLpro, RdRp, PLpro, and S, were the four functional proteins in 2019-nCoV that were examined as potential drug targets. Currently, there is no identified and approved antiviral drug for treatment of COVID-19. However, due to the impact it has had globally, there is a significant research push is now underway to repurpose existing drugs and to design new therapeutic agents targeting various components of the virus5. Evidently, the most efficient method to construct ant-2019-nCoV drug is to screen drugs which are currently being used in the clinic. RNA-dependent RNA polymerase (RdRp) is an imperative protease that catalyzes the replication of RNA from RNA template and is therefore an attractive therapeutic target for coronavirus. Hence, from the aforementioned effects of HDAC inhibitors on viral infections, it prompted us to further study and examine its ability to act as inhibiters for RNA-dependent RNA polymerase (RdRp) of COVID-19, *via in silico* method using molecular docking studies, with the aim of ultimately finding an effective treatment against COVID-19 infections.

Methods and Materials

Sequence alignment and modeling

Most of the promising clinical trials for COVID-19 treatments highlighted that the main antivirus drugs focus on proteins such as 3CLpro and RdRp which are much more preserved in SARS-COV and 2019-nCOV, specifically relating to its functionality. Therefore, our docking study focus on Rpdp as an important target. SARS-CoV-2 genes has been shown to share nucleotide identity and 89.10% nucleotide similarity with SARS-CoV genes in recent studies [35,36]. The SARS-HCoV resolved configuration (PDB ID: 6NUR) was used for binding, having a 97.08% sequence identity to SARS-CoV-2 RdRp. 6NUR is a SARS-HCoV non-structural protein 12 (nsp12) solved structure (cryo-electron microscopy) [37]. Moreover, Remdesivir was used as a control in this study, given it was the antagonist of 2019-COV RdRp.

Molecular docking methodology

Docking analysis was carried out by means of the Discovery Studio 2.5 software (Accelrys Inc., San Diego, CA, USA). Completely automatic docking tool using "Dock ligands (CDOCKER)" procedure operating on Intel (R) core (TM) i32370 CPU @ 2.4 GHz 2.4 GHz, RAM Memory 2 GB under the Windows 7.0 system. Furthermore, these docked compounds were assembled using a software Chem 3D ultra 12.0 [Chemical Structure Drawing Standard; Cambridge Soft corporation, USA (2010)], and then sent to the Discovery Studio 2.5 software. From this, an automatic protein formulation procedure was conducted through the MMFF94 forcefield with the binding

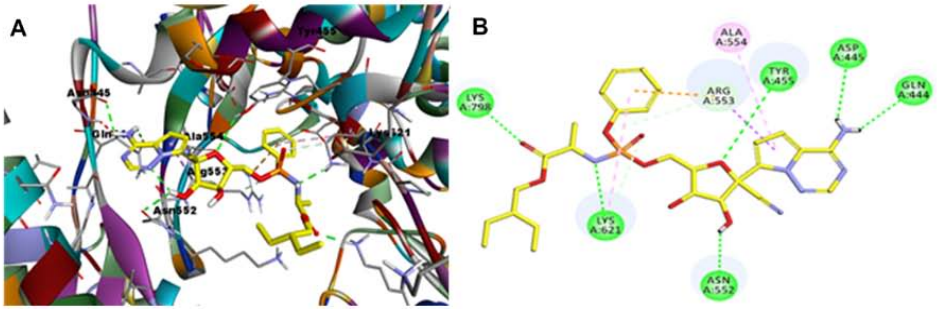

Figure 5: 3D (A) and 2D (B) The active site of SARS-CoV-2 RdRp within the binding stage of (PDB entry: 6NUR).

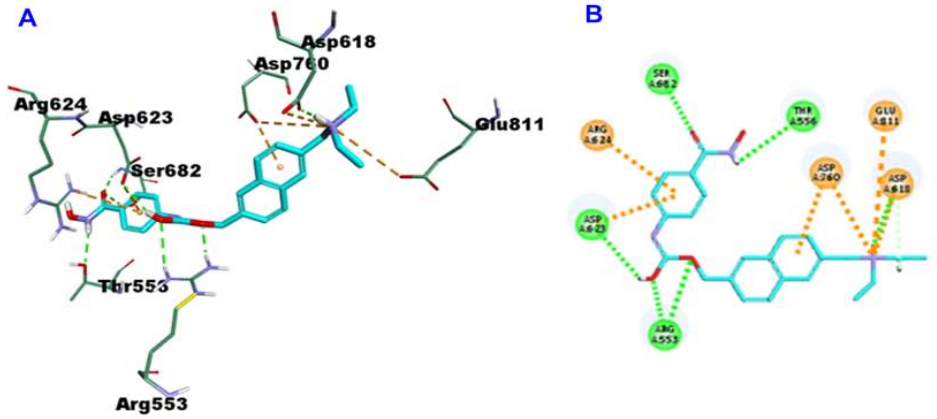

Figure 6: 3D (A) and 2D (B) binding mode of Givinostat into the active site of SARS-CoV-2 RdRp (PDB entry: 6NUR).

site sphere recognized by the software. The receptor was recorded as "input receptor molecule" in the CDOCKER protocol explorer. Establishing this, force fields were applied on the test compounds to obtain the minimum lowest energy structure. These poses were ranked and studied thoroughly, showing the best ligand-HDAC interactions from the calculations and 2D and 3D examinations [38-41].

Molecular dynamic simulation

The Nanoscale Molecular Dynamics (NAMD) software was used in the molecular dynamic simulation (MDS) to understand the ligand-enzyme complexes [42]. This was done by using the force field from the CHARMM27 [43]. Hydrogen atoms were added to the protein structures utilizing the psfgen plugin included Antibiotics 2020, 9, 562 14 of 16 in the Visual Molecular Dynamic (VMD) 1.9 software [44]. Subsequently, the entire framework was solvated using TIP3P water particles and 0.15M NaCl. This was carried out by minimizing the energy of the systems and then pprogressivel heating it up to 300 K and reach equilibrium for 200 seconds. Thereofore, the MDS was proceeded for 50 ns, and the trajectory was collected every 0.1 ns and further investigated with the VMD 1.9 software. These outputs were collected every 0.1 ns so that the conformational changes of the entire system can be considered using the Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF). From this, the VMD Force Field Toolkit (ffTK) [44] and an online software Ligand Reader & Modeler was used to examine the topologies and parameters of the compounds tested (http://www.charmm-gui.org/?doc=input/ligandrm) [45].

Binding free energies were calculated through the free energy perturbation (FEP) technique, which was performed using the web-based software Absolute Ligand Binder [46].

Results and Discussion

Molecular modeling

RdRp: In order to investigate binding affinity between protein and the HDACIs, Discovery Studio software package was used. Twelve HDACIs were selected for the present study, the six approved HDACIs (SAHA, Romidepsin (FK228) and its active metabolite (RedF), Belinostat, Pracinostat, Panobinostat and Chidamide). In addition to five HDACIs in clinical trials, Recolinostat, Givinostat, Tacedinaline, Mocetinostat and Entinostat and comparing these results with the remdesivir.

The docking protocol was started by the docking of remdesivir in the SARS-HCoV solved structure (PDB ID: 6NUR, chain A). As shown in Figure 5, Table 1, remdesivir formed 6-H bonds with Gln444, Asn552, Asp445, Tyr455, Lys621 and Lys798, in addition to hydrophobic interaction with Ala554, Lys621 and Arg553. The CDOCKER energy of remdesivir is -30.1162 and the CDOCKER interaction energy is -59.1337.

Among the twelve virtually screened HDAC inhibitors, five compounds; Romidepsin (FK228) and its active metabolite (RedF), Pracinostat, Panobinostat and Givinostat displayed CDOCKER energy and CDOCKER interaction energy better than the control drug remdesivir.

Table 1: CDOCKER energies and the energies produced from interactions, as well as the amount of hydrogen bonds of HDACIs into the active site of SARS-HCoV solved structure (PDB ID: 6NUR).

Ligands	CDOCKER energy	CDOCKER interaction energy	No. of H-Bond
RedFK	-40.3907	-53.7436	8
Romidepsin	-35.9163	-52.8092	7
SAHA	-38.9654	-41.914	6
Belinostat	-28.8614	-43.0371	7
Pracinostat	-37.1318	-63.7588	6
Panobinostat	-45.8189	-50.0363	6
Chidamide	-33.2602	-44.6772	6
Tacedinaline	-32.2461	-40.437	5
Givinostat	-36.8399	-65.0395	7
Mocetinostat	-33.4505	-42.9723	5
Recolinostat	-36.001	-48.8773	5
Entinostat	-42.5925	-48.5569	6
Remdesivir	-30.1162	-59.1337	6

Givinostat, with -36.8399 CDOCKER energy and -65.0395 CDOCKER interaction energy, 7 hydrogen bonds were incorporated in the formation alongside amino acid remains Arg553 (2-H bonds), Thr556, Asp618, Asp623, Ser682 (2-H bonds). In addition to three strong attractive charges with Asp618, Asp760 and Glu811 and many other hydrophobic interactions with Asp618, Asp623, Arg624 and Asp760 (Figure 6).

Regarding Pracinostat (Figure 7), with -37.1318 CDOCKER energy and -63.7588 CDOCKER interaction energy, it engaged in the formation of 6-H bonds with Lys545 (2-H bonds), Arg553 (2-H bonds), Arg555 and Tyr613 amino acid residues. In addition to eight hydrophobic interactions; two strong attractive charges with Asp618 and Asp760, two Pi-anion interactions with Asp623 and others with Tyr455, Tyr619, asp623, Asp618 and Asp760.

As shown in Figure 8, Romidepsin active metabolite (RedF), with -40.3907CDOCKER energy and -53.7436 CDOCKER interaction energy, incorporated in the formation of 8-H bonds with the amino acid residues Arg553 (4-H bonds), Arg555, Thr556, Asp618 and Asp623, in addition to three hydrophobic interactions with Thr455, Lys545 and Arg624.

Romidepsin, with -35.9163 CDOCKER energy and -52.8092 CDOCKER interaction energy, engaged in 7-H bonds with the amino acid residues Arg553 (3-H bonds), Lys551 (2-H bonds), Lys621 and Lys798, On top of three hydrophobic interactions alongside Aps618, Lys621 and Arg624 (Figure 9).

Panobinostat, with -45.8189 CDOCKER energy and -50.0363 CDOCKER interaction energy, it involved in the formation of 6-H bonds with Lys545, Arg553 (2-H bonds), Arg555 (2-H bonds) and Asp623 amino acid remainders. On top of many hydrophobic interactions with Asp618, Lys621, Cys622 and two salt bridge interactions with Asp760 (Figure 10).

Furthermore, all remaining virtually screened HDAC inhibitors; SAHA, Belinostat, Chidamide, Tacedinaline, Mocetinostat,

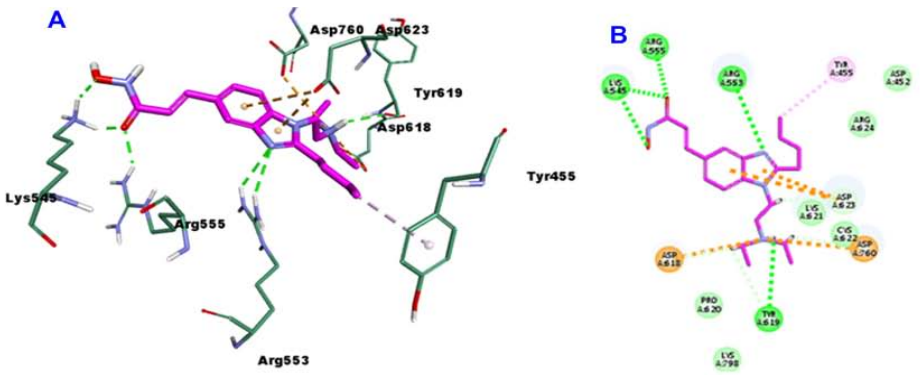

Figure 7: 3D (A) and 2D (B) binding mode of Pracinostat into the active site of SARS-CoV-2 RdRp (PDB entry: 6NUR).

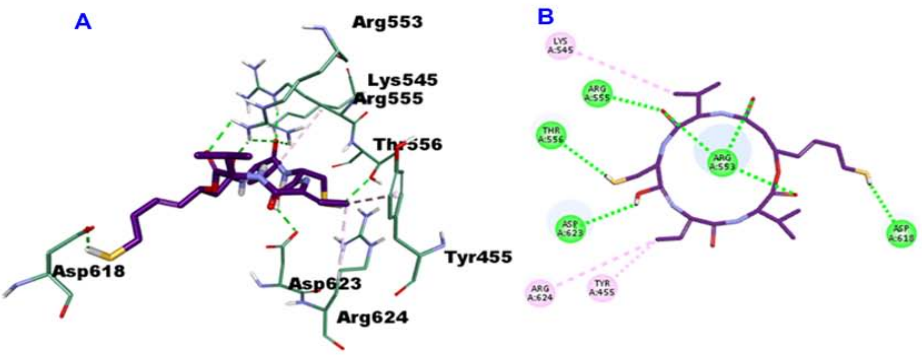

Figure 8: 3D (A) and 2D (B) binding mode of Romidepsin active metabolite (RedF) into the active site of SARS-CoV-2 RdRp (PDB entry: 6NUR).

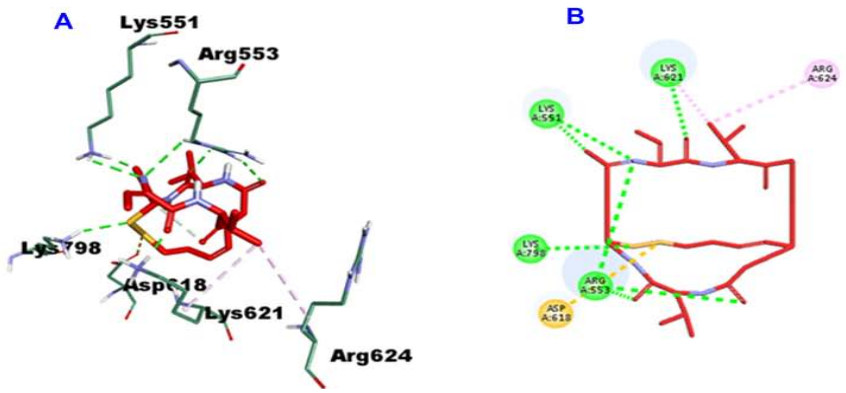

Figure 9: 3D (A) and 2D (B) binding mode of Romidepsin into the active site of SARS-CoV-2 RdRp (PDB entry: 6NUR).

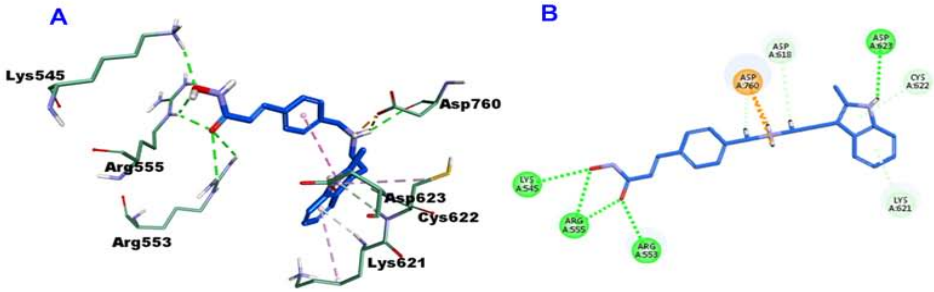

Figure 10: 3D (A) and 2D (B) binding mode of Panobinostat into the active site of SARS-CoV-2 RdRp (PDB entry: 6NUR).

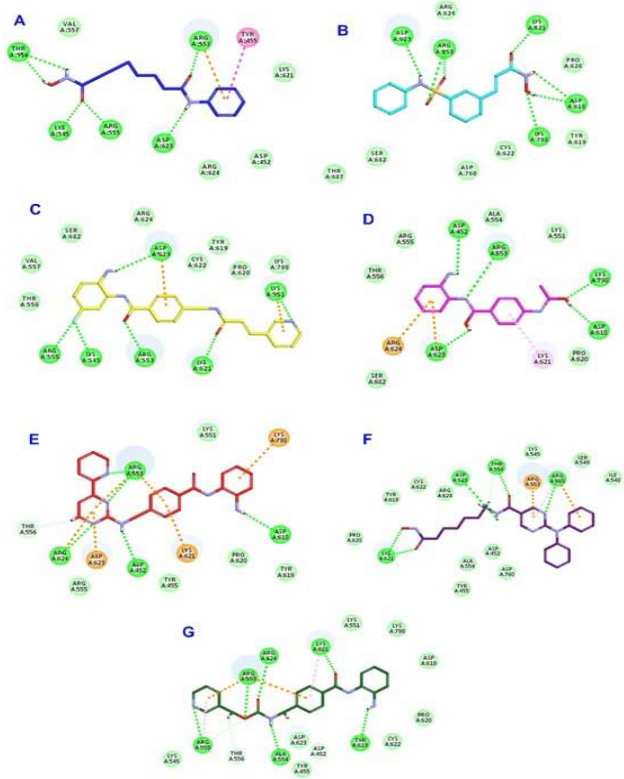

Figure 11: 2D binding mode of SAHA (A), Belinostat (B), Chidamide (C), Tacedinaline (D), Mocetinostat (E), Recolinostat (F) and Entinostat (G) into the active site of SARS-CoV-2 RdRp (PDB entry: 6NUR).

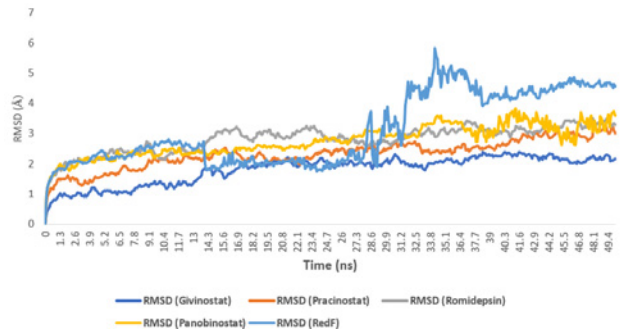

Figure 12: MDS-derived RMSDs of the top-scoring compounds inside the protein's active site over 50 ns.

Recolinostat, Entinostat, showed remarkable CDOCKER energy and CDOCKER interaction energy and involved in 5- or 6-H bonds as shown in Table 1 and Figure 11.

Molecular dynamic simulation analysis

To further validate our docking experiments, we subjected the protein-ligand complexes of the top-scoring compounds (Table 1) to a series of 50 ns Molecular Dynamic Simulations (MDS) (Figure 12). Givinostat achieved the highest binding stability inside the protein's active site with a standard RMSD value of 1.8 Å, and plateaued at 14.2 ns. The next most stable drug was pracinostat (RMSD = 2.3 Å) which was able to achieve equilibrium (plateau) at 28.7 ns.

Both romidepsin and panobinostat showed almost identical binding stability inside the protein's active site (RMSD = 2.81 and 2.74 Å, respectively), where they reached the plateau at 24.7 ns.

Regarding the romidepsin's metabolite RedF, its binding position was stable and similar to romidepsin and panobinostat till 13.8 (RMSD = 2.65 Å). Afterward, its RMSD decreased to about 2.1 Å till 27.7 ns. Starting from this point, the compound's binding mode changed and its RMSD suddenly increased to reach its peak at 34.2 ns (RMSD = 5.84 Å). Subsequently, this transient increase of RMSD was stabilized at 4.2 Å from 38.4 ns till the end of the MDS. Hence, this compound was the least stable compound with an average RMSD of 3.1 Å.

Conclusion

In essence, the docking study revealed that the virtually screened approved HDAC inhibitors or in clinical trials of possible effective activity to be repurposed as COVID-19 SARS-CoV-2 RdRp inhibitors. This will encourage the examination of these drugs as anti-COVID-19, in particular, Givinostat, Pracinostat, Panobinostat, Romidepsin (FK228) and its active metabolite (RedF), as they bind tightly to the enzymes and displayed lowest CDOCKER energy and CDOCKER interaction energy better than or very close to the control drug remdesivir. This will be added to its HDAC inhibition activity. Hopefully, Givinostat, Pracinostat, Panobinostat, Romidepsin (FK228) and its active metabolite (RedF) could be promising candidates for COVID-19 RNA-dependent RNA polymerase (RdRp) inhibitors. Significantly, these inhibitors should be evaluated on their effectivity when treating COVID-19, specifically using the drugs that have been approved for clinical trials with limited toxicity.

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