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MOLECULAR DOCKING STUDY REVEALS THE POTENTIAL REPURPOSING OF HISTONE DEACETYLASE INHIBITORS AGAINST COVID-19

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ABSTRACT: The outburst of new coronavirus (COVID-19) infections, firstly appeared in Wuhan in 2019, has massively expanded to the whole world. At the end of March 2020, the rapid spread of the infection happened in about 206 countries around the globe. At the moment, the statistics of WHO on coronavirus pandemic revealed total infected cases of 21,770,000 and more than 77,000 deaths all over the world, with no proven antiviral agent available yet to control COVID-19 infection. The world is currently in desperate need of finding potent therapeutic agents. Histone deacetylases (HDACs) represent one of the most promising viral targets. Importantly, HDACs are critical factors involved in the control of viral replication. The molecular mechanisms associated with underlying the role of HDACs in viral latency, viral reactivation, and carcinogenesis are progressively disclosed. Till now, six HDACIs anticancer drugs have been approved by the FDA. Herein, in the *in-silico* structure-based drug design approach was utilized to identify novel structural characteristics for the potential repurposed activity of HDACIs as antivirals for COVID-19. In this respect, 12 HDACIs were carefully screened to probe their possible anti-viral activity against SARS-CoV main proteaseM^{pro} (PDB: 6LU7). Most of the screened HDACIs are strongly bind into the active binding site of crystallographic structure of M^{pro} (PDB: 6LU7) with comparable docking energy and hydrogen bond formation. These findings demonstrate that HDACIs, especially Romidepsin and its active form (RedFK), hold promise as COVID-19 protease inhibitors. Moreover, calculations of physicochemical parameters and drug-likeness properties of the screened compounds implied an acceptable ADMET for all tested compounds.

INTRODUCTION: In the last few weeks of 2019, an unprecedented global outbreak of novel coronavirus (COVID-19) (2019-nCoV; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, detected firstly in Wuhan, China in patients having severe pneumonia [1-5].

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As of February 2020, 2019-nCoV has rapidly spread over 25 countries across four continents, with more than 40,000 cases that have been confirmed with a mortality risk of ~2% [6]. At the end of March 2020, a massive spread of the infection took place in about 206 countries across the globe; about 1,000,000 patients and 50,000 deaths occurred [World Health Organization. Coronavirus disease 2019 (COVID-19): situation report, 65. (2020)]. In the absence of any tested and certified antiviral agent for COVID-19 infection, medical professionals have utilized supportive care to cover the infection.

Current research work in this area suggests that certain drugs with the appropriate viral restraining mechanisms may give rise to promising results. However, new inventions are expected to take months to years to develop a new vaccine [7]. Therefore, drug repurposing of the approved drugs is urgently needed. Discovery of known drug that inhibits the COVID-19 virus main protease (M^{pro}) will result in a crucial role in controlling viral replication and transcription [8]. Zhenming Jin, *et al.*, resolved the crystal structure of COVID-19 virus M^{pro} in complex comprising N3 ligand [9-11]. The polypeptides functional groups are released from the polyproteins by extensive proteolytic processing, mainly by a 33.8-kDa main protease (M^{pro}), also referred to as the 3C-like protease. M^{pro} consumes the polyprotein at no less than 11 conserved sites, starting with the autolytic cleavage of this enzyme itself from pp1a and pp1ab [12]. The functional importance of M^{pro} in the viral life cycle, together with the absence of closely related homologues in humans, identify the M^{pro} as an attractive target for antiviral drug design for the purpose of finding potential COVID-2019 3C-like Protease Inhibitors [13].

On the other hand, the use of targeted agents could be a promising strategy for optimizing antiviral therapies. Histone deacetylases (HDACs) is one of the most important validated targets. (HDACs) and histone acetyltransferases (HATs) modulate acetylation of lysine residues **Fig. 1** in histones and non-histone proteins [14]. HATs transfer the acetyl group *via* acetyl-CoA, and HDACs/SIRTs deacetylate ε-N-acetylated lysine residues using Zn^{2+} (HDACs) or NAD^{+} (SIRTs) as cofactors [15].

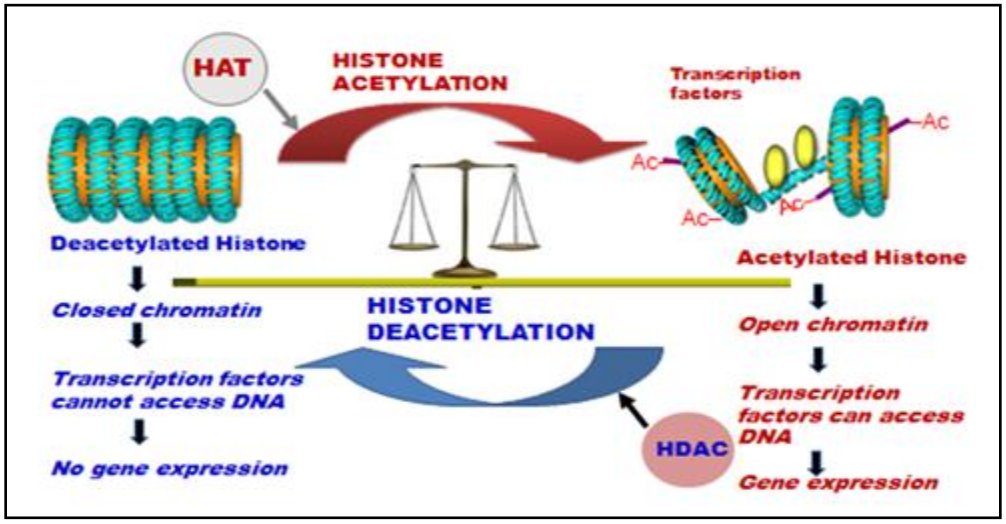


FIG. 1: HATS AND HDACS REGULATE GENE TRANSCRIPTION THROUGH THE MODULATION OF NUCLEOSOMAL PACKAGING OF DNA

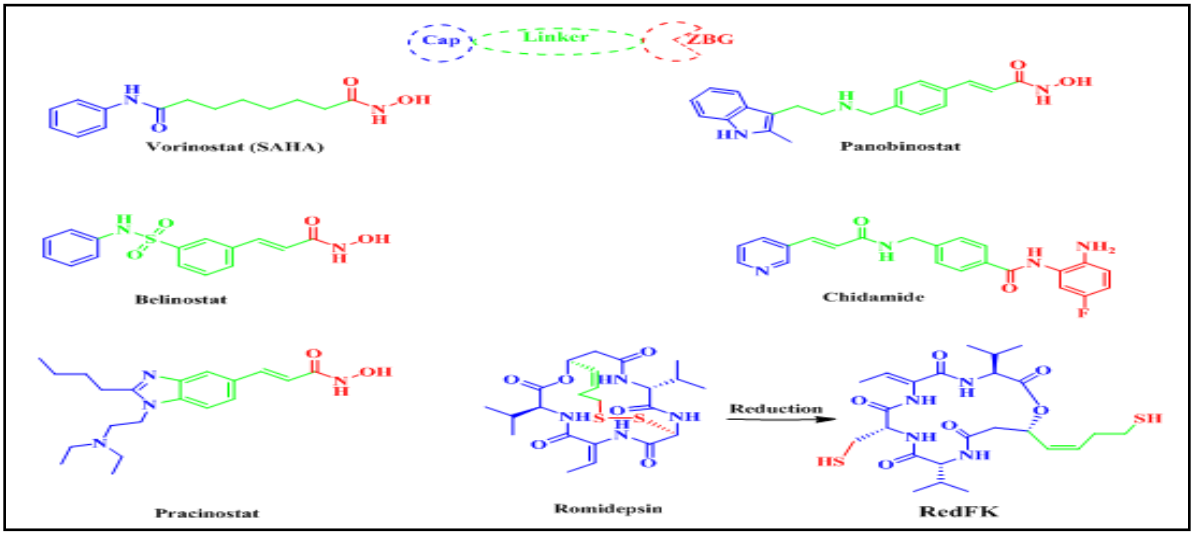


FIG. 2: STRUCTURE OF THE APPROVED ANTICANCER HDACIs

There are three common functional and pharmacophore patterns for the design of HDAC inhibitors that have been recognized and represented as: A) Cap, B) linker and C) zinc-binding group (ZBG) [16] as shown in **Fig. 2**. Recently, six HDAC inhibitors **Fig. 2** have been approved as anticancer agents, namely; Vorinostat (SAHA), Romidepsin (FK228), and its active metabolite RedFK, Belinostat (PXD101), Pracinostat, Panobinostat (LBH-589) and Chidamide (CS055) [15-19].

In addition, many others are in clinical trials such as Recolinostat, Givinostat, Tacedinaline, Mocetinostat, and Entinostat **Fig. 3** [20-25].

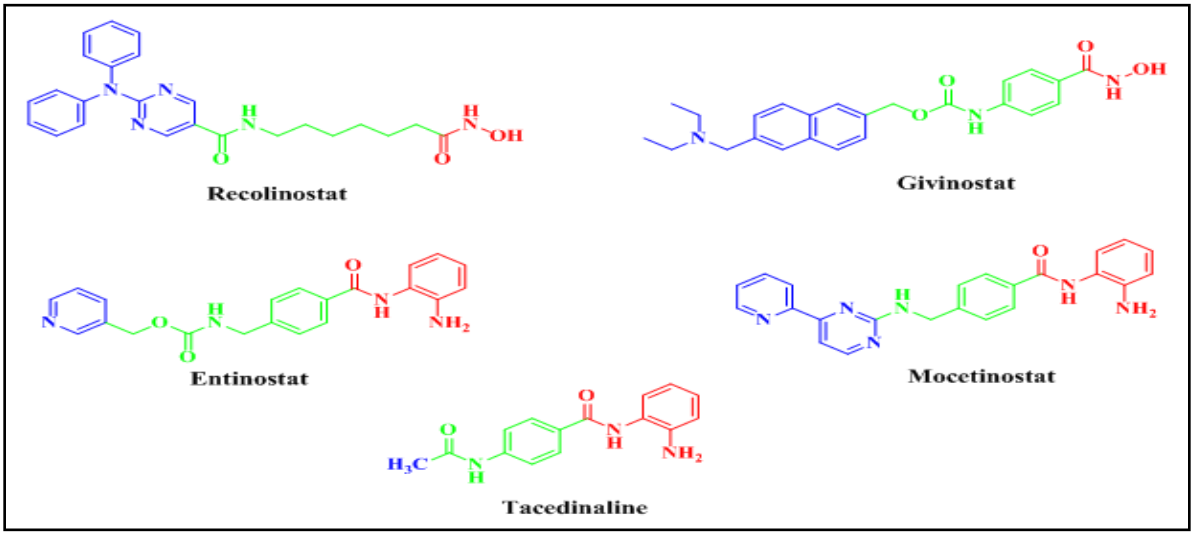
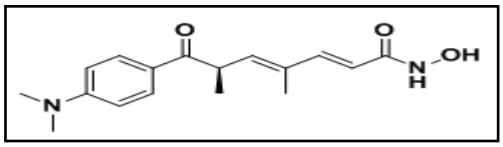


FIG. 3: STRUCTURE OF SOME ANTICANCER HDACIs IN CLINICAL TRIALS

HDACIs have been widely employed in psychiatry and neurology as mood stabilizers and anti-epileptics and recently, they have been intensively investigated and utilized for treatments of cancer, parasitic and inflammatory diseases [26, 27]. Of particular relevance to present work, HDACs play a significant role in viral replication; therefore HDAC inhibitors have a potential role as novel therapeutic targets in viral infections [28, 29]. The HDACIs, Trichostatin A and valproic acid, were found to suppress the expression of innate antiviral molecules such as IFNβ, interferon-simulated genes, and proteins involved in TLR3/TLR4 signaling.

Also, these compounds suppressed microglial and astrocytic cytokine and chemokine gene expression, but with different effects on different groups of cytokines [30]. Furthermore, Pan-HDAC inhibitors such trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA), and valproic acid (VPA) block the zinc-containing catalytic domain of HDACs [31]. In addition, TSA minimizes the number of viral genomes in Herpes Simplex Virus-1 infected cells [32]. SAHA activates HIV-I from latency period [33].

Notably, respiratory syncytial virus (RSV) reduced histone acetylation by enhancing HDAC2 expression; a research study using the HDACIs trichostatin A and SAHA showed that these drugs inhibit RSV replication and decreased RSV-induced airway inflammation and oxidative stress. These HDACIs constitute a promising approach in modulating lung inflammation associated with this viral infection [34].

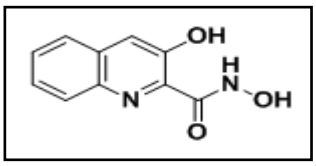


Trichostatin A

More importantly, after the successful initial round of in vitro research in January 2013, the Danish Research Council awarded the research team led by Dr. Ole Søgaard from the Danish Aarhus University Hospital the amount of $2 million to commence clinical trials on 15 humans. The aim is for HDAC inhibitors to eliminate HIV from the reservoirs it builds within the DNA of infected cells, followed by vaccination to assist the immune system to neutralize any replicating virus [35].

As for the purpose of reactivating latent HIV, and hence diminishing the reservoirs, panobinostat, entinostat, romidepsin, and vorinostat are specifically used. Vorinostat was noted as the least potent of the HDAC inhibitors in this trial36. Another study found that romidepsin led to a higher and more sustained level of cell-associated HIV RNA reactivation than vorinostat in latently infected T-cells *in-vitro* and *ex-vivo* [37].

A related investigation demonstrated that hydroxamic acid derivative (BMY-26270) is a selective inhibitor of purified influenza A, as well as the RNA-dependent RNA polymerase (RdRp) with IC_{50} = 40 µM. Similarly, it can inhibit influenza B in an equal potency along with the *in-vitro* capped RNA-dependent transcription of influenza B viral polymerase with equal potency [38, 39].



BMY-26270

Based upon the aforementioned effects of HDACIs on viral infections and our ongoing interest in finding novel targets to control CoV infections, the main objective of the present work is to repurpose known FDA-approved HDACIs as potential COVID-2 agents. This requires studying the *in-silico* structure-based drug design approach to probe the physicochemical properties and the required structural features for the potential repurposed antiviral activity of HDACIs into the active binding site of the crystallographic structure of M^{pro} (PDB: 6LU7).

Experimental:

Docking Studies:

Optimization of Target Compounds: The target compounds were built up into a 3D model. After inspecting their structures and the formal charges on atoms by 2D depiction, the following steps were undertaken: The docked compounds were drawn using Chem. 3D ultra 12.0 software [Chemical Structure Drawing Standard; Cambridge Soft Corporation, USA (2010)], and copied to Discovery Studio 2.5 software. Force fields are applied to the selected compounds to obtain the minimum lowest energy structure.

Docking of the Target Molecules to the Active Binding Site of Crystallographic Structure of M^{pro} (PDB: 6LU7): Discovery Studio 2.5 software (Accelrys Inc., San Diego, CA, USA) was used for docking analysis. Fully automated docking tool using "Dock ligands (CDOCKER)" protocol running on Intel (R) core (TM) i32370 CPU @ 2.4 GHz 2.4 GHz, RAM Memory 2 GB under the Windows 7.0 system [40-43]. The X-ray crystallographic structure of M^{pro} complexed with N3 ligand was obtained from the Protein Data Bank through the internet (http://www. rcsb.org/, PDB code: 6LU7) [9]. The enzyme was prepared for docking studies *via* an automatic protein preparation module that was used for applying CHARMm force field. The binding site sphere has been defined automatically by the software.

Now, the above-prepared receptor is given as input for "input receptor molecule" parameter in the CDOCKER protocol parameter explorer. The obtained poses were studied and the poses showing best ligand-HDAC interactions were chosen and employed for CDOCKER energy (protein-ligand interaction energies) calculations. Finally, receptor-ligand interactions of the complexes were investigated in 2D and 3D styles.

RESULTS AND DISCUSSION:

Docking Study Results: In order to investigate the binding affinity between protein and the HDACIs, Discovery Studio software package was used. Twelve HDACIs were selected for the present study, including the six approved HDACIs (SAHA, Romidepsin (FK228) and its active metabolite (RedF), Belinostat, Pracinostat, Panobinostat and Chidamide), and five HDACIs in clinical trials, namely Recolinostat, Givinostat, Tacedinaline, Mocetinostat, and Entinostat. The obtained results are compared with those of the N3 ligand.

Validation of the docking protocol was undertaken by re-docking of the ligand N3 in M^{pro} crystal structures. The RMSD value was less than 0.926 (less than 2), thereby reflecting a great trust in the produced docking results. It is clearly established that N3 ligand, as shown in **Fig. 4**, engaged in six hydrogen bonds with amino acid residues Phe140, His163, Clu166 (three HB), and Gln189in addition to many hydrophobic interactions.

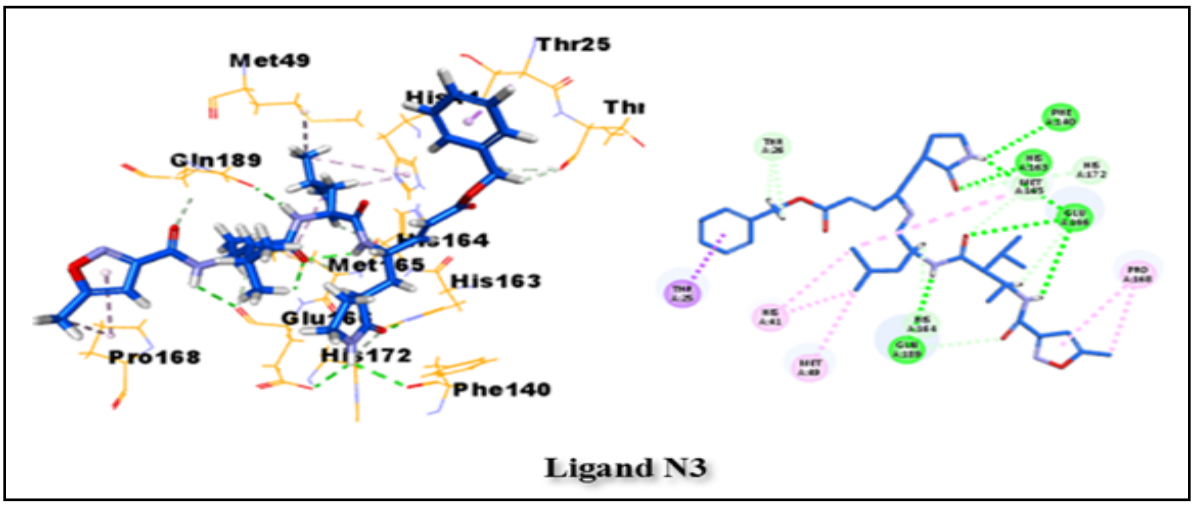


FIG. 4: DOCKING AND BINDING MODE OF LIGAND N3 INTO THE ACTIVE SITE OF THE SARS M^{pro} STRUCTURE (PDB ID: 6LU7)

Out of the six approved tested HDACIs, Romidepsin and active metabolite (RedFK) are the most promising drugs as they can strongly bound to the substrate-binding pocket of the SARS polymerase structure (PDB ID: 6LU7) and showed significant inhibition with lower docking score as compared to standard drug **Table 1**. RedFK surprisingly shows the best docking score (-52.8463) and engaged with seven hydrogen bonds with the amino acid residues Asn142, Gly143, His163, His164, Clu166, and Gln189, in addition to many hydrophobic interactions with His41, Met49, Cys145, and Met165 **Fig. 5, Table 1**.

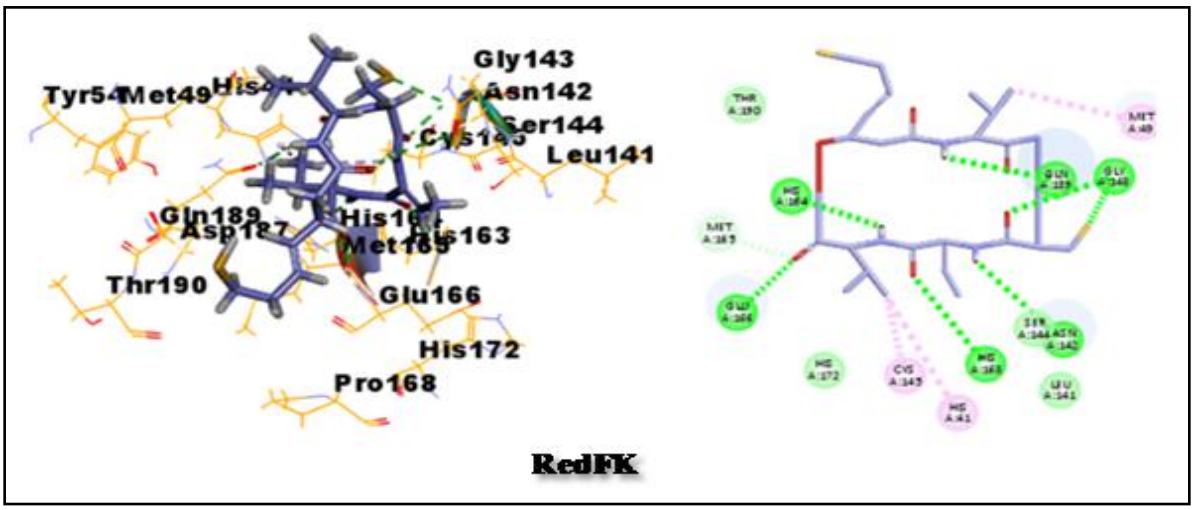


FIG. 5: DOCKING AND BINDING MODE OF REDFK INTO THE ACTIVE SITE OF THE SARS M^{pro} STRUCTURE (PDB ID: 6LU7)

Romidepsin **Fig. 6, Table 1** showed low interaction energy (-51.0786) and formed six hydrogen bonds with Asn142, Gly143, Clu166 (2), and Gln189 (2). Also, Romidepsin forms many hydrophobic interactions with His41, Asn142, Cys145, His163, Met165.

On the other hand, SAHA, Belinostat, Panobinostat, and Chidamide, all of them are preferentially binds to the substrate-binding pocket of the SARS polymerase structure (PDB ID: 6LU7) and are incorporated in five hydrogen bonds while Pracinostat was engaged in 4 hydrogen bonds **Table 1**.

Regarding the five HDACIs in a clinical trial, Tacedinaline was the most promising one with six hydrogen bonds with His41, Gly143, Met165, Glu166, Arg188, and Gln189, in addition to many hydrophobic interactions with Met49, Cys145, and Met165 **Fig. 7**, **Table 1**.

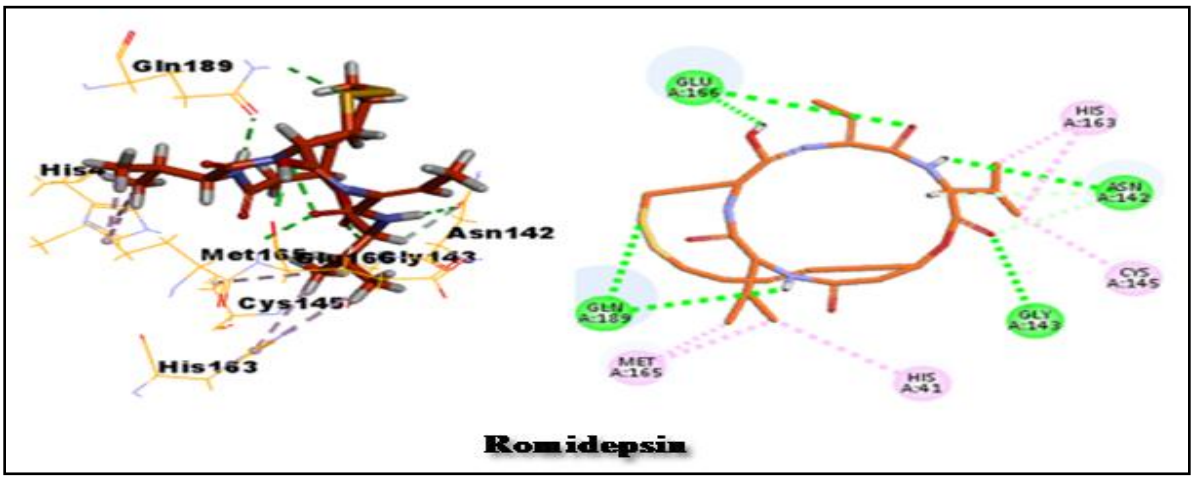


FIG. 6: DOCKING AND BINDING MODE OF ROMIDEPSIN INTO THE ACTIVE SITE OF THE SARS M^{pro} STRUCTURE (PDB ID: 6LU7)

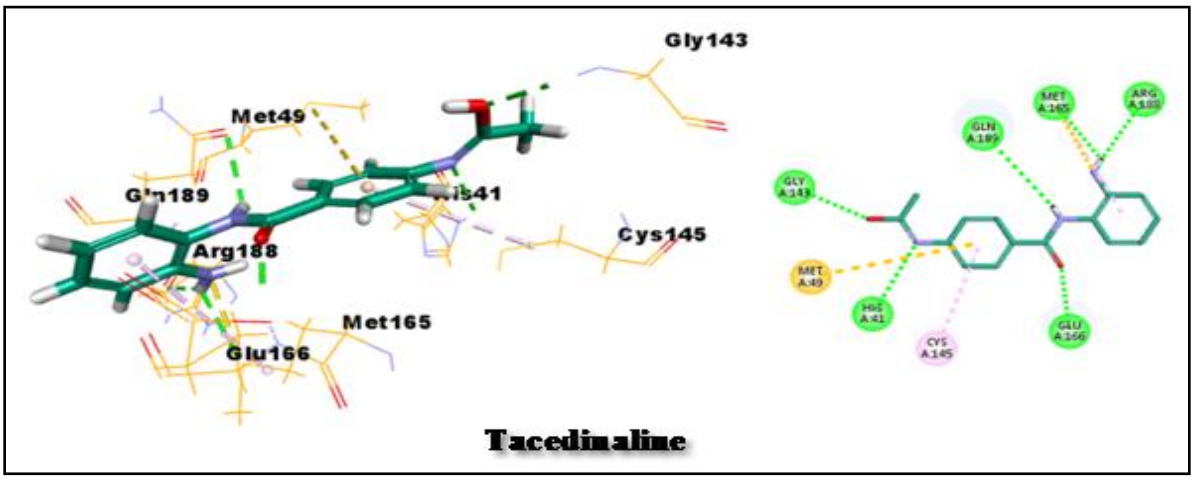


FIG. 7: DOCKING AND BINDING MODE OF TACEDINALINE INTO THE ACTIVE SITE OF THE SARS M^{pro} STRUCTURE (PDB ID: 6LU7)

Givinostat gave the lowest interaction energy (-55.77) **Fig. 8, Table 1,** and incorporated in five hydrogen bonds with the amino acid residues Thr26 (2), Ser144, and His163 (2) in addition to hydrophobic interactions with Phe140, Gly143, Cys145, and Glu166. Mocetinostat incorporated in five hydrogen bonds, while Recolinostat and Entinostat both of them incorporated in four hydrogen bonds **Table 1**.

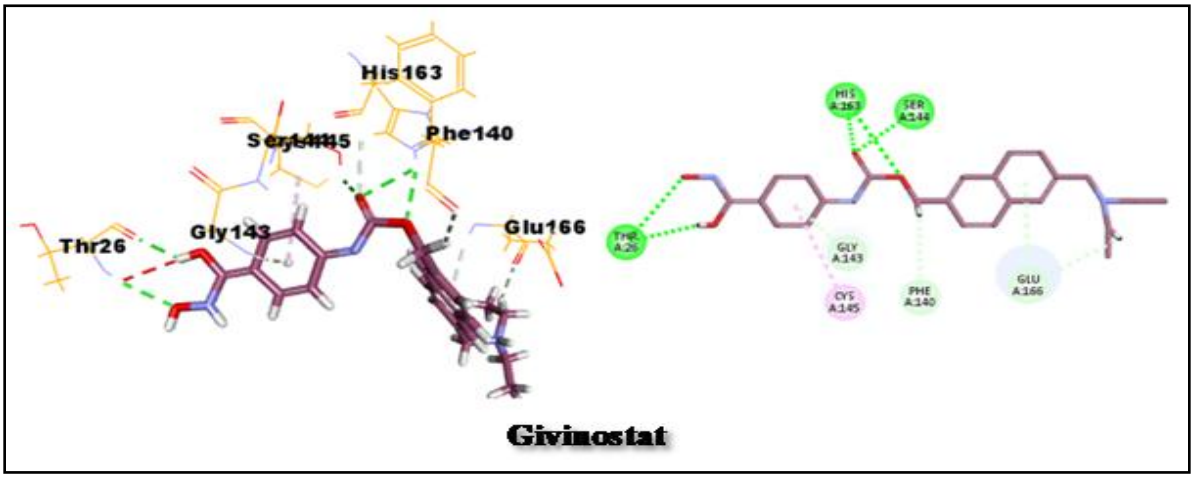


FIG. 8: DOCKING AND BINDING MODE OF GIVINOSTAT INTO THE ACTIVE SITE OF THE SARS M^{pro} STRUCTURE (PDB ID: 6LU7

TABLE 1: LOWEST INTERACTION ENERGIES, THE NUMBER OF HYDROGEN BOND AND HYDROPHOBIC INTERACTIONS OF HDACIS INTO THE ACTIVE SITE OF THE SARS M^{pro} STRUCTURE (PDB ID: 6LU7)

Ligands	CDOCKER interaction energy	No. of H-Bond	H-Bonds Interacting Residues	Other Interacting Residues
RedFK	-52.8463	7	Asn142, Gly143, His163, His164, Clu166, Gln189	His41, Met49, Cys145, Met165
Romidepsin	-51.0786	6	Asn142, Gly143, Clu166 (2), Gln189 (2)	His41, Asn142, Cys145, His163, Met165
SAHA	-43.0314	5	Phe140, Ser144, His163 (2), Glu166	Met165
Belinostat	-37.8126	5	His41, Glu166, Thr190 (2), Gln192	His41, Met165, Pro168, Gln189
Pracinostat	-51.6866	4	Gly143, Ser144, Cys144, Glu166	Met165, Glu166, Leu167, Pro168
Panobinostat	-47.5979	5	His41, Gly143, Ser144, Cys144, Glu166	Met165, Glu166, Pro168
Chidamide	-41.9816	5	Asn142, Ser144, His163, Glu166 (2)	Cys145, Gln189
Tacedinaline	-35.0394	6	His41, Gly143, Met165, Glu166, Arg188, Gln189	Met49, Cys145, Met165
Givinostat	-55.7796	5	Thr26 (2), Ser144, His163 (2)	Phe140, Gly143, Cys145, Glu166
Mocetinostat	-42.7216	5	Gly143, Met165 (2), Glu166 (2)	His41, Asn142, Met165, Pro168
Recolinostat	-47.2529	4	Gly143, Ser144, His163, Glu166	Met165, Glu166, Gln189
Entinostat	-44.9487	4	Gly143, Cys145, Glu166, Leu167	Cys145
N3	-79.0435	6	Phe140, His163, Clu166 (three) Gln189	Thr25, Thr26, His41, Met49, Met165, Glu166, Pro168, His172,

Physicochemical Characterization: Physico-chemical characterization of drugs is an essential parameter in drug design strategies. For drug molecule to reach its target, it should pass through different barriers that are either lipophilic membranes or hydrophilic aqueous media having different pH's. The drug also must have suitable pharmacokinetics to achieve an acceptable pattern of ADMET. For a new drug to exert biological activity, it should achieve binding with enzyme or receptor and induce changes in these protein structures and hence efficacy. The most important parameters for drug action are topological parameters like strain energy, radius, Wiener index [44]. Diameter, molecular mass and Wiener index are also considered as steric parameters while Log P, Gibbs free energy, molar refractivity and heat of formation are the thermodynamic parameters. The thermodynamic and steric parameters have a great role in binding with the receptor sites. Moreover, Wiener index can give an indication of the Van der Wall areas and compactness of the molecule [45]. A QSAR study on the physicochemical parameters and their effect on HDAC inhibitory activity revealed that lipophilicity is an important parameter in cap and spacer, which should be hydrophobic. In addition, the zinc-binding group should be hydrophilic and with suitable volume for binding with the enzyme**.** Molar refractivity and molar volume can also affect the activity, while electronic factors are not very essential [46].

Another research study indicated that the mercaptoacetamide based HDACISs had enhanced lipophilicity, permeability, and solubility [47]. Although the hydroxamic acid group has the best affinity to HDAC enzyme among other zinc-binding groups, it is necessary to find other zinc-binding groups with better physicochemical properties [48]. Moreover, *in-vitro* and *in-vivo* studies revealed a direct correlation between pharmacokinetics and pharmacodynamics for sires of a mercaptoacetamide based HDACIs with antitumor activity [49]. The low bioavailability of hydroxamic acid motivated scientists to replace it with benzamid zinc-binding group, and therefore, the physicochemical properties were improved as a result of the replacement of the cap moiety of Trichosatin with pyridyl moiety [50].

Consequently, it seems important to calculate the most important physicochemical properties and drug-likeness represented in Lipinski's rule [51] of these nominated drugs for the purpose of repurposing as potential COVID-19 molecules.

From the results in **Table 2**, it is obvious that all the selected compounds obey the rule of five, Lipinski's rule, and have good drug-like properties. Most of the molecular masses are below 500. Optimum lipophilicity of the screened compounds represented in calculated log P, with log P range from 1.018 to 4. No more than 5 hydrogen bond donors (HBD) and no more than 10 hydrogen bond acceptors available in these compounds. The Gibbs free energy is negative in the case of Romidepsin and its active metabolite RedFK, indicating that the complex formation between these two compounds

and potential target enzymes is spontaneous. The Wiener index calculation has an indication of the possibility of the formation of hydrophobic Van Der Waal bonding with the potential target site. In view of these findings, it is clearly established that the calculated parameters should be considered in the repurposing design of the selected compounds in COVID-19.

TABLE 2: CALCULATED PHYSICOCHEMICAL PARAMETERS OF DIFFERENT HDACIS USING CHEM3D 16 SOFTWARE

#	Name	Molecular Mass	Molecular Topology: Wiener Index	Topological Diameter bond(s)	Molar refractivity, Cm^3/mol	Clog P	Gibbs Free Energy kJ/mol]	HBD	HBA	Lipinski's Rule
1	Vorinostat (SAHA)	264.147	954	14	7.361	1.784	87.59	3	3	264.147; 3; 3; 10; 0.989
2	Panobinostat	349.179	2128	17	10.769	3.008	0	4	4	349.179; 4; 4; 8; 2.643
3	Belinostat	318.067	1160	13	8.668	1.990	0	3	4	318.067; 4; 3; 6; 1.177
4	Chidamide	390.149	2874	18	11.290	2.482	353.45	3	5	390.149; 5; 3; 8; 1.857
5	Pracinostat	358.237	1842	14	10.829	3.231	0	2	5	358.237; 5; 2; 11; 3.212
6	Romidepsin	540.694	3504	11	14.398	1.856	-145.65	4	5	540.208; 5; 4; 2; 3.443
7	RedFK	542.223	3773	14	14.575	2.158	-136.39	6	5	542.223; 5; 6; 6; 3.07
8	Rocilinostat	433.211	3677	19	12.329	3.702	651.86	3	6	433.211; 6; 3; 13; 3.481
9	Givinostat	421.200	3442	20	12.082	4.054	310.84	3	4	421.2; 4; 3; 11; 2.658
10	Entinostat	376.153	2622	18	10.686	2.231	307.35	3	4	376.154; 4; 3; 9; -0.118
11	Mocetinostat	396.169	3031	18	11.658	2.854	891.44	3	6	396.17; 6; 3; 7; 2.174
12	Tacedinaline	269.116	917	12	7.769	1.018	229.27	3	3	269.116; 3; 3; 5; 0.736
13	Trichostatin A	302.163	1252	14	9.081	2.298	293.61	2	4	302.163; 4; 2; 7; 1.926

CONCLUSION: The overall findings of this work revealed that the already approved HDACIs or in clinical trials are of potential potent activity to be repurposed as COVID-19$CoVM^{pro}$inhibitors. This will stimulate the evaluation of these drugs as anti-COVID-19, especially Romidepsin and its active form (RedFK), which showed the highest score of binding with the binding site of the $CoVM^{pro}$ structure (PDB ID: 6LU7). This behavior will be added to its HDAC inhibition activity. Finally, we believe that this study will open up new avenues in the repurposing a drug for the treatment of COVID-19, especially these drugs have been approved or used in clinical practices with limited toxicity, and therefore, we recommend that they should be taken into consideration in the treatment of COVID-19.

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CONFLICTS OF INTEREST: Nil

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