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Original Article

Molecular modeling of some commercially available antiviral drugs and their derivatives against SARS-CoV-2 infection

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Abstract

Numerous prior studies have identified therapeutic targets that could effectively combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, including the angiotensin-converting enzyme 2 (ACE2) receptor, RNA-dependent RNA polymerase (RdRp), and Main protease (Mpro). In parallel, antiviral compounds like abacavir, acyclovir, adefovir, amantadine, amprenavir, darunavir, didanosine, oseltamivir, penciclovir, and tenofovir are under investigation for their potential in drug repurposing to address this infection. The aim of the study was to determine the effect of modifying the functional groups of the aforementioned antivirals in silico. Using the genetic optimization for ligand docking algorithm on software Maestro (version 11.1), the modified antivirals were docked onto ACE2 receptor, RdRp, and Mpro. Using QuickProp (Maestro v11.1), PASS (prediction of activity spectra for the substances), and altogether with SwissADME, the ADMET (absorption, distribution, metabolism, excretion, and toxicity) of the modified antivirals, as well as their bioavailability and the predicted activity spectra, were determined. Discovery studio software was used to undertake post-docking analysis. Among the 10 antivirals, $N(CH_3)_2$ derivative of darunavir, $N(CH_3)_2$ derivative of amprenavir and NCH_3 derivative of darunavir exhibited best binding affinities with ACE2 receptor (docking scores: -10.333, -9.527 and -9.695 kJ/mol, respectively). Moreover, NCH_3 derivative of abacavir (-6.506 kJ/mol), NO_2 derivative of didanosine (-6.877 kJ/mol), NCH_3 derivative of darunavir (-7.618 kJ/mol) exerted promising affinity to Mpro. In conclusion, the results of the in silico screenings can serve as a useful information for future experimental works.

Keywords: ACE2, Antiviral derivatives, Mpro, RdRP, SARS-CoV-2

Introduction

The novel severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is the main concerning issue in the 2nd decade of the 21st century due to its rapid transmission and attack rates. The World Health Organization (WHO) declared the coronavirus diseases 2019 (COVID-19), which is caused by SARS-CoV-2, as a pandemic on 11 March 2020 [1-3]. Even after the pandemic, SARS-CoV-2 is anticipated to cause a significant problem to health sector. Like previous viral outbreaks, including hepatitis B, hepatitis C, Zika virus, Ebola virus, malaria, human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), continue to present persistent and significant public health

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challenges [4-6]. While the SARS-CoV-2 virus is primarily known for its impact on the respiratory system [7-10], there has been a noted rise in the incidence of cardiovascular diseases and type 2 diabetes mellitus among both pediatric and adult populations [11,12].

The coronavirus family is characterized by a multitude of spike proteins essential for gaining entry into host epithelial cells. Specifically, the angiotensin-converting enzyme 2 (ACE2), an enzyme within the human body, serves as a receptor site for the crown-like spike protein of the virus, facilitating authorized access of the virus into host cells [13,14]. Following the complex formation between the spike protein and ACE2 on the cellular membrane, the viral spike protein is cleaved by the transmembrane protease, serine 2 (TMPRSS2), aiding the fusion stage that eventually leads to viral entry. Like other RNA viruses, upon entering the host cells, SARS-CoV-2 requires RNA-dependent RNA polymerase (RdRp) for replication [15-17]. Other than that, the viral replication also requires SARS-CoV-2 main protease (Mpro) to convert large polyproteins into functional proteins necessary. Thus, anti-SARS-CoV-2 drugs have been developed by focusing on the aforementioned proteins including monoclonal antibodies, nirmatrelvir, remdesivir, and nirmatrelvir [18-20]. Previously, several structures of RdRp in complex with substrate RNA and remdesivir were reported, providing insights into the mechanisms of RNA recognition by RdRp [21]. These structures also reveal the mechanism of RdRp inhibition by nucleotide inhibitors and offer a molecular template for the development of RdRp-targeting drugs [21]. RdRp is an important viral enzyme in the life cycle of RNA viruses, therefore it has been targeted in a variety of viral diseases, including hepatitis C virus, Zika virus, and coronaviruses [13,14,22-28]. With two consecutive and surface-accessible aspartates in a beta-turn structure, the active RdRp site is highly conserved [29].

Throughout the early COVID-19 pandemic, there were no authorized medications, and the FDA (the United States Food and Drug Administration) recommended hundreds of natural drugs based on previous reports [23]. Herein, we have performed in silico studies comprising of molecular docking, prediction of activity spectra for the substances (PASS), and ADMET (absorption, distribution, metabolism, excretion, and toxicity) analyses. The study focused on computationally prepared derivatives from 10 commercially available antivirals, namely abacavir [30], acyclovir [31], adefovir [32], amantadine [33], amprenavir [34], darunavir [35], didanosine [36], oseltamivir [37], penciclovir [38], and tenofovir [39]. The aim of this study was to investigate whether modifying the functional groups of the aforementioned antivirals could improve their activities against SARS-CoV-2-associated target proteins.

Methods

Derivatives preparation

To prepare the derivatives, abacavir, acyclovir, adefovir, amantadine, amprenavir, darunavir, didanosine, oseltamivir, penciclovir, and tenofovir were used as mother ligand molecules, respectively. The functional group of each mother ligand molecule was substituted by Cl, F, NCH_3, $N(CH3)_2$, OH^-, NH^{2-}, $HOOC^-$, or NO^- [40]. Since there were no methods to predict which functional group that could increase the antiviral activity, its selection was based on 'trial and error' principles.

Molecular docking

Protein preparation Nand receptor grid generation

The glide of Schrödinger-Maestro (version 11.1) was used for molecular docking analysis to predict the behavior of the aforementioned compounds [41]. The antiviral targets, retrieved from protein data bank (PDB), were SARS-CoV-2 Mpro (PDB id: 5RGX), human ACE2 (PDB id: 4OW0), RdRp (PDB id: 5KHR). A Quasi-Newton approach was used to optimize the ligand placement in the molecular docking which was initiated on random points around the receptor site. After retrieved from the PDB, the 3D crystal structure of each protein was prepared using Schrödinger-Maestro (version 11.1) with the following settings: pH 7.0±2.0; water < 3; and minimized protein-ligand complex under OPLS3 force field. Grid box of each protein was

generated on PockDrug, with 10 Å length in each of X-, Y-, and Z- axis for determining the binding site using Receptor Grid Generation.

Ligand preparation and docking

Ligands were prepared for docking study using LigPrep process generating possible state at target pH 7.0±2.0 and the complex was kept under OPLS3 force field. Thereafter, flexible ligand docking was performed on Schrödinger-Maestro (version 11.1,) with penalties imposed on non-cis/trans amide bonds. Glide % was used to calculate the final score, which was based on energy-saving positions. The best-docked position with the lowest Glide score value was recorded for each ligand. The antiviral activity of the selected compounds against Mpro, ACE2, and RdRp was investigated using molecular docking experiments [42].

ADMET prediction

ADMET properties of selected best-docked ligand molecules were predicted using QuickProp feature in Maestro (version 11.1), while bioavailability and absorption parameters were estimated using an online software, SwissADME [43]. Herein, molecular descriptors such as molecular weight, hydrogen bond acceptor, hydrogen bond donor, LogP (lipophilicity), molar refractivity, number of rotatable bonds, topological polar surface area and five violations of Lipinski's rule were measured. The analysis was performed because orally active drugs should comply with these commonly used druglike properties as they indicate the safety and efficacy potentials [41].

In silico prediction of activity spectra for substances

The computer program PASS was used to predict the antiviral activity of the antiviral derivatives. The program calculates a compound's expected activity spectrum as probable activity (Pa) and probable inactivity (Pi). Pa and Pi have values ranging from 0.000 to 1.000, where a compound is considered active if Pa>Pi. Cut-offs of Pa>0.7, Pa>0.5, and Pa<0.5 were used to indicate strong, moderate, and weak levels of likelihood for pharmacological activity, respectively. The analysis was carried out using an online platform, molinspiration (Way2Drug).

Results

Molecular docking study against SARS-CoV-2

Some modified molecules were recently subjected to receptor-based molecular docking. A broad range of docking scores was discovered during DFT's molecular docking research. F-, Cl-, NCH_3-, $N(CH_3)_2$-, OCH_3-, NO_2-, and OH-modified derivatives of oseltamivir, tenofovir, penciclovir, didanosine, darunavir, amprenavir, adefovir, acyclovir were investigated to for their docking scores, where the results are presented in **Table 1**. $N(CH_3)_2$ derivatives of darunavir and amprenavir had the highest docking scores of -10.333 and -9.527 kJ/mol against ACE2, respectively. Darunavir, amprenavir, and didanosine had a relatively increased docking score after the modification with all modifying functional groups.

Table 1. Docking scores of modified antivirals against ACE2, Mpro, and RdRp

Compounds	Docking score (kJ/mol)		
	ACE2	Mpro	RdRp
Abacavir	-6.917	-5.729	-7.293
Cl derivative of abacavir	-5.974	-5.418	-6.640
F derivative of abacavir	-6.558	-5.678	-6.699
$N(CH_3)_2$ derivative of abacavir	-6.117	-6.427	-8.035
$N(CH_3)$ derivative of abacavir	-6.896	-6.506	-7.281
$O(CH_3)_2$ derivative of abacavir	-6.701	-5.166	-6.476
Acyclovir	-6.146	-5.333	-6.109
Cl derivative of acyclovir	-5.752	-5.245	-5.381
F derivative of acyclovir	-6.026	-5.501	-5.433
$N(CH_3)$ derivative of acyclovir	-7.078	-5.486	-5.688
$N(CH_3)_2$ derivative of acyclovir	-6.749	-5.440	-6.462
$O(CH_3)$ derivative of acyclovir	-5.409	-4.797	-5.048
Adefovir	-6.545	-5.922	-6.336
Cl derivative of adefovir	-6.492	-4.604	-5.779

Compounds	Docking score (kJ/mol)		
	ACE2	Mpro	RdRp
F derivative of adefovir	-5.738	-3.945	-5.785
$N(CH_3)_2$ derivative of adefovir	-7.218	-4.861	-5.533
$N(CH_3)$ derivative of adefovir	-7.366	-4.82	-5.160
$O(CH_3)$ derivative o adefovir	-6.651	-4.701	-4.984
Amantadine	-3.852	-4.303	-5.485
$N(CH_3)_2$ derivative of amantadine	-4.086	-4.568	-5.920
$N(CH_3)$ derivative of amantadine	-3.713	-4.431	-5.843
NO_2 derivative of amantadine	-4.106	-4.789	-6.019
$O(CH_3)$ derivative of amantadine	-3.646	-5.123	-5.153
OH derivative of amantadine	-4.62	-4.734	-5.708
Amprenavir	-7.013	-6.302	-6.971
Cl derivative of amprenavir	-9.312	-6.927	-7.537
F derivative of amprenavir	-8.903	-6.034	-8.933
$N(CH_3)_2$ derivative of amprenavir	-9.527	-7.768	-7.931
$N(CH_3)$ derivative of amprenavir	-8.004	-7.067	-6.532
$O(CH_3)$ derivative of amprenavir	-7.75	-6.084	-7.566
Darunavir	-6.233	-5.357	-6.933
Cl derivative of darunavir	-8.391	-6.786	-7.376
$N(CH_3)$ derivative of darunavir	-9.695	-7.618	-7.151
$N(CH_3)_2$ derivative of darunavir	-10.333	-6.975	-6.360
NO_2 derivative of darunavir	-8.248	-6.928	-6.440
$O(CH_3)$ derivative of darunavir	-5.785	-6.81	-6.996
Didanosine	-6.309	-5.248	-7.703
Cl derivative of didanosine	-7.637	-5.670	-6.357
F derivative of didanosine	-7.662	-5.857	-6.442
NO_2 derivative of didanosine	-6.772	-6.877	-6.871
$O(CH_3)$ derivative of didanosine	-5.753	-5.469	Not applicable
OH derivative of didanosine	-6.676	-6.349	-5.624
Oseltamivir	-5.545	-5.852	-7.044
$N(CH_3)_2$ derivative of oseltamivir	-3.314	-5.916	-6.185
$N(CH_3)$ derivative of oseltamivir	-5.706	-6.038	-7.115
NO_2 derivative of oseltamivir	-3.962	-6.234	-6.368
$O(CH_3)$ derivative of oseltamivir	-5.254	-5.524	-6.258
OH derivative of oseltamivir	-6.356	-5.743	-6.073
Tenofovir	-7.529	-5.878	-5.839
Cl derivative of tenofovir	-5.931	-5.398	-6.506
$N(CH_3)_2$ derivative of tenofovir	-6.022	-5.242	-7.149
$N(CH_3)$ derivative of tenofovir	-6.083	-5.065	-6.264
NO_2 derivative of tenofovir	-5.41	-5.072	-6.803
OH derivative of tenofovir	-6.832	-6.181	-5.695
Penciclovir	-6.095	-5.455	-6.404
$N(CH_3)_2$ derivative of penciclovir	-5.998	-6.107	-7.007
$N(CH_3)$ derivative of penciclovir	-7.591	-5.705	-7.430
NO_2 derivative of penciclovir	-5.196	-6.007	-6.284
$O(CH_3)_2$ derivative of penciclovir	-5.426	-5.033	-5.325
OH derivative of penciclovir	-5.814	-5.524	-5.987

ADMET and PASS prediction

The QuickProp feature in Maestro 11.1 and a web-based software, SwissADME, were used to analyze the pharmacokinetic and pharmacodynamic characteristics of the natural compounds with the best conformations. Modified molecules with the best scores were chosen based on "Lipinski's Rule of Five", where the predicted absorption and bioavailability are presented in **Table 2** and **Table 3**. All antiviral derivatives were revealed to possess antiviral activity in PASS analysis performed on molinspiration (Way2Drug), where the results are presented in **Table 3**. The pharmacokinetic and pharmacodynamic properties of the antiviral derivatives suggest their adequacy for being drug-like molecules, thus having potentials as novel medications.

Table 2. ADMET study of selected bioactive compounds ant their derivatives

Compounds	MW	HBA	HBD	LogP	AMR	TPSA	Lipinski's violations
Rule	<500 (g/mol)	≤10	≤5	≤5	40–130	≤140 (Å^2)	≤1
Cl derivative of abacavir	334.80	4	2	3.03	90.14	90.88	0
F derivative of abacavir	318.35	5	2	2.97	85.09	90.88	0
$N(CH_3)_2$ derivative of abacavir	314.39	5	4	3.15	90.21	79.10	0
$N(CH_3)$ derivative of abacavir	300.36	4	3	2.70	85.31	87.89	0
$O(CH_3)_2$ derivative of abacavir	300.36	4	2	2.83	85.13	90.88	0
Cl derivative of acyclovir	273.68	5	2	1.25	65.42	108.05	0
F derivative of acyclovir	257.22	6	2	1.17	60.36	108.05	0
$N(CH_3)$ derivative of acyclovir	239.23	5	3	0.80	60.58	105.06	0
$N(CH_3)_2$ derivative of acyclovir	253.26	5	2	1.51	65.48	96.27	0
$O(CH_3)$ derivative of acyclovir	239.23	5	2	0.89	60.41	108.05	0
Cl derivative of adefovir	321.66	7	2	1.27	72.42	135.19	0
F derivative of adefovir	305.20	8	2	1.16	67.36	135.19	0
$N(CH_3)_2$ derivative of adefovir	301.24	7	2	0.69	72.48	123.41	0
$N(CH_3)$ derivative of adefovir	287.21	7	3	0.00	67.58	132.20	0
$O(CH_3)$ derivative o adefovir	287.21	7	2	1.14	67.41	135.19	0
$N(CH_3)_2$ derivative of amantadine	179.30	1	0	2.70	56.39	3.24	0
$N(CH_3)$ derivative of amantadine	165.28	1	1	2.48	51.49	12.03	0
NO_2 derivative of amantadine	181.23	2	0	1.79	51.98	45.82	0
$O(CH_3)$ derivative of amantadine	181.27	2	1	2.65	52.57	21.26	0
OH derivative of amantadine	167.25	2	2	1.97	47.41	32.26	0
Cl derivative of didanosine	270.67	5	2	1.34	63.78	93.03	0
F derivative of didanosine	254.22	6	2	1.00	58.73	93.03	0
NO_2 derivative of didanosine	283.24	7	3	1.06	74.94	137.72	0
$O(CH_3)$ derivative of didanosine	250.25	5	1	1.41	63.50	82.03	0
OH derivative of didanosine	238.24	5	3	0.64	66.12	91.90	0
$N(CH_3)_2$ derivative of oseltamivir	340.46	5	1	3.66	94.32	67.87	0
$N(CH_3)$ derivative of oseltamivir	326.43	5	2	3.04	89.92	76.66	0
NO_2 derivative of oseltamivir	342.39	6	1	2.26	89.91	110.45	0
$O(CH_3)$ derivative of oseltamivir	312.45	5	2	3.59	89.12	73.58	0
OH derivative of oseltamivir	314.42	6	3	3.13	85.48	93.81	0
$N(CH_3)_2$ derivative of penciclovir	281.31	5	3	1.47	75.17	107.27	0
$N(CH_3)$ derivative of penciclovir	267.28	5	4	0.89	70.27	116.06	0
NO_2 derivative of penciclovir	283.24	7	3	0.18	69.78	149.85	0
$O(CH_3)_2$ derivative of penciclovir	281.31	5	2	1.21	74.83	108.05	0
OH derivative of penciclovir	267.28	5	3	0.76	70.10	119.05	0
Cl derivative of tenofovir	321.66	7	3	0.72	72.49	146.19	0
$N(CH_3)_2$ derivative of tenofovir	315.27	7	2	1.44	77.29	123.41	0
$N(CH_3)$ derivative of tenofovir	301.24	7	3	0.89	72.38	132.20	0
NO_2 derivative of tenofovir	317.20	9	2	0.20	71.90	165.99	1
OH derivative of tenofovir	288.22	7	4	0.00	69.01	153.13	1

AMR: molar refractivity; HBA: hydrogen bond acceptor; HBD: hydrogen bond donor; LogP: lipophilicity; MW: molecular weight; TPSA: topological polar surface area.

Table 3. PASS results and predicted absorption and bioavailability of antiviral derivatives

Compounds	Pa	Pi	Absorption	Bioavailability
Cl derivative of abacavir	0.501	0.003	High	0.55
F derivative of abacavir	0.955	0.002	High	0.55
$N(CH_3)_2$ derivative of abacavir	0.599	0.004	High	0.55
$N(CH_3)$ derivative of abacavir	0.598	0.004	High	0.55
$O(CH_3)_2$ derivative of abacavir	0.590	0.004	High	0.55
Cl derivative of acyclovir	0.679	0.011	High	0.55
F derivative of acyclovir	0.845	0.002	High	0.55
$N(CH_3)$ derivative of acyclovir	0.818	0.004	High	0.55
$N(CH_3)_2$ derivative of acyclovir	0.836	0.004	High	0.55
$O(CH_3)$ derivative of acyclovir	0.820	0.004	High	0.55
Cl derivative of adefovir	0.823	0.004	High	0.55
F derivative of adefovir	0.926	0.002	High	0.55
$N(CH_3)_2$ derivative of adefovir	0.832	0.003	High	0.55
$N(CH_3)$ derivative of adefovir	0.789	0.003	High	0.56
$O(CH_3)$ derivative o adefovir	0.836	0.004	High	0.55
$N(CH_3)_2$ derivative of amantadine	0.633	0.013	High	0.55
$N(CH_3)$ derivative of amantadine	0.652	0.010	High	0.55
NO_2 derivative of amantadine	0.734	0.002	High	0.55
$O(CH_3)$ derivative of amantadine	0.548	0.004	High	0.55
OH derivative of amantadine	0.645	0.011	High	0.55
Cl derivative of amprenavir	0.678	0.004	High	0.55
F derivative of amprenavir	0.679	0.004	High	0.55
$N(CH_3)_2$ derivative of amprenavir	0.694	0.004	High	0.55
$N(CH_3)$ derivative of amprenavir	0.703	0.004	High	0.55
$O(CH_3)$ derivative of amprenavir	0.739	0.004	High	0.55
Cl derivative of darunavir	0.841	0.004	High	0.55
$N(CH_3)$ derivative of darunavir	0.843	0.004	High	0.55
$N(CH_3)_2$ derivative of darunavir	0.839	0.004	High	0.55
NO_2 derivative of darunavir	0.872	0.004	High	0.55
$O(CH_3)$ derivative of darunavir	0.897	0.003	High	0.55
Cl derivative of didanosine	0.800	0.003	High	0.55
F derivative of didanosine	0.989	0.001	High	0.55
NO_2 derivative of didanosine	0.644	0.005	Low	0.55
$O(CH_3)$ derivative of didanosine	0.851	0.002	High	0.55
OH derivative of didanosine	0.818	0.004	High	0.55
$N(CH_3)_2$ derivative of oseltamivir	0.855	0.002	High	0.55
$N(CH_3)$ derivative of oseltamivir	0.908	0.002	High	0.55
NO_2 derivative of oseltamivir	0.882	0.002	High	0.55
$O(CH_3)$ derivative of oseltamivir	0.878	0.002	High	0.55
OH derivative of oseltamivir	0.930	0.001	High	0.55
$N(CH_3)_2$ derivative of penciclovir	0.547	0.006	High	0.55
$N(CH_3)$ derivative of penciclovir	0.530	0.007	High	0.55
NO_2 derivative of penciclovir	0.528	0.007	High	0.55
$O(CH_3)_2$ derivative of penciclovir	0.711	0.003	High	0.55
$O(CH_3)$ derivative of penciclovir	0.826	0.002	High	0.55
Cl derivative of tenofovir	0.917	0.002	High	0.55
$N(CH_3)_2$ derivative of tenofovir	0.906	0.003	High	0.56
$N(CH_3)$ derivative of tenofovir	0.872	0.004	High	0.56
NO_2 derivative of tenofovir	0.914	0.003	Low	0.11
OH derivative of tenofovir	0.852	0.004	Low	0.55

Discussion

Since the early phase of COVID-19 pandemic, researchers have tried developing anti-SARS-CoV-2 with clinical trials for drugs repurposing being approved by the FDA. The list of clinical trials of several antivirals along with their target of action are presented in **Table 4**. To screen potent antiviral candidate, particularly in the field of structural molecular biology and computer-aided drug design, molecular docking stands as a pivotal technique. This approach aids to predict an active compound, based on the ligand binding with the target protein [44]. According to the molecular docking results in the present study (**Table 1**), most of the derivatives were revealed to have higher docking scores compared to their respective parent compounds such as amprenavir, darunavir, didanosine and tenofoviraginst when targeting ACE2 receptor [45], Mpro, and RdRp [46,47].

Table 4. Clinical trials of antivirals during the initial phase of COVID-19 pandemic

Drugs name	Target of action	Countries where the drugs were being tested or approved	References
Abacavir	Replication inhibitory effect	Italy (recommended), Thailand, and China	[48]
Acyclovir	Inhibition of viral DNA polymerase through phosphorylation; viral protease enzyme; expressions of multiple other viral genes; and RNA-dependent RNA polymerase	Africa and the United States of America	[49,50]
Amantadine	Inhibition of e-channel conductance in reconstituted lipid bilayers and prevention of the viral RNA release into the host cell	Denmar, Poland, and Kuwait	[33,51]
Darunavir	Inhibition of the Main protease	China and Italy	[35,52]
Oseltamivir	Neuraminidase inhibitor	United Kingdom	[53]
Tenofovir	Nucleotide analog	Spain	[54]

During the previous outbreaks caused by Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), antiviral targeting ACE2 receptor and Mpro have been used for the infection treatment [55-58]. Mpro is particularly interesting, not only because of its main role in the post-translational stage, but also because of its sequence similarity with that observed in SARS-CoV [59]. Further, RdRp which possess a critical function in the life cycle of RNA viruses, but has no counterpart in the host cell, is also considered as an important potential target for the antivirals. Nucleoside analogs in the form of adenine or guanine derivatives were previously reported to inhibit RdRp, including that in human coronaviruses [60,61]. In the present study, we found that the parent drugs and their derivative were potential in interacting with the aforementioned target proteins. Among 10 antivirals investigated herein, derivatives from darunavir had relatively higher docking score, where their visualized interactions with the target protein are presented in **Figure 1**.

Herein, we observed the ligand-protein complex was formed involving multiple amino acids and types of interaction. For the interaction between NCH_3 derivative of abacavir and Mpro or RdRp, amino acids involved were Cus306, Arg200, Leu3I4, Phe415, Tyr448, and Ser368. As for the interaction between NO_2 derivative of amantadine and RdRp occurred through multiple bindings (such as conventional hydrogen bond, carbon hydrogen bond and pi-alkyl bond) involving Arg200, Pro197, Phe415, Met414, Tyr448, and Cts366. NCH_3-modified abacavir, OCH_3-modified amantadine, NO_2-modified didanosine interacted with Cys145 through pi carbon and pi sulfur bond. $N(CH_3)$ and $N(CH_3)_2$ derivatives of darunavir had docking scores of -9.695 and -10.333 kJ/mol, respectively, involving van der Waals, conventional hydrogen bond, carbon hydrogen bond, and alkyl bond interactions through Tyr269, Lys158, Pro248, Val188, Gly161, Asn110, Ile223, Pro224, Gln 233, Tyr208, Asp165, Val166, and Ala247. F and $N(CH_3)_2$ derivatives of amprenavir had docking scores of -9.312 and -9.527n kJ/mol, respectively, where the interaction occurred at Met207, Tur274, Asp165, Pro248, Lys158, Glu162, and Leu163 through hydrogen bond, carbon hydrogen bond, alkyl and pi alkyl bond. NCH_3 derivative of darunavir, F derivative of amprenavir, and NO_2 derivative of oseltamivir established van der Walls or pi-amine interactions at Glu166. Amino acids Ala247, Met209, Asp165, Tyr274, Asn268, and Gly267 were involved in the complex formation between NCH_3 derivative of acyclovir and ACE2 receptor (7.078 kJ/mol). Lastly, NCH_3 derivative of acyclovir, OCH_3 derivative of adefovir, NCH_3 derivative of penciclovir, and OH derivative of Tenofovir the interaction occure at Cys145 and Glu166.

Docking scores are considered good if they agree (semi) quantitatively with binding free energies. Positive binding energy is superior to negative binding energy. The stronger or more stable the protein-ligand complex, the more negative the binding. When the protein and ligand come together, the score resembles the potential energy shift. This implies that a very negative value indicates a strong binding, whereas a less negative or even positive score indicates a weak

or non-existent binding. In addition, according to the second rule of thermodynamics, the total entropy of a system either grows or remains constant in every spontaneous event, where it never declines. Since protein-ligand interactions occur continually during molecular docking, more entropy is produced as a negative docking score. The majority of ligands in this present study have a bioavailability score of 0.55 or 0.56. In accordance with a previous study, the value range indicates favorable pharmacokinetic qualities [62]. Moreover, in the present study, there were only a few antiviral derivatives that had low absorption rate (**Table 3**).

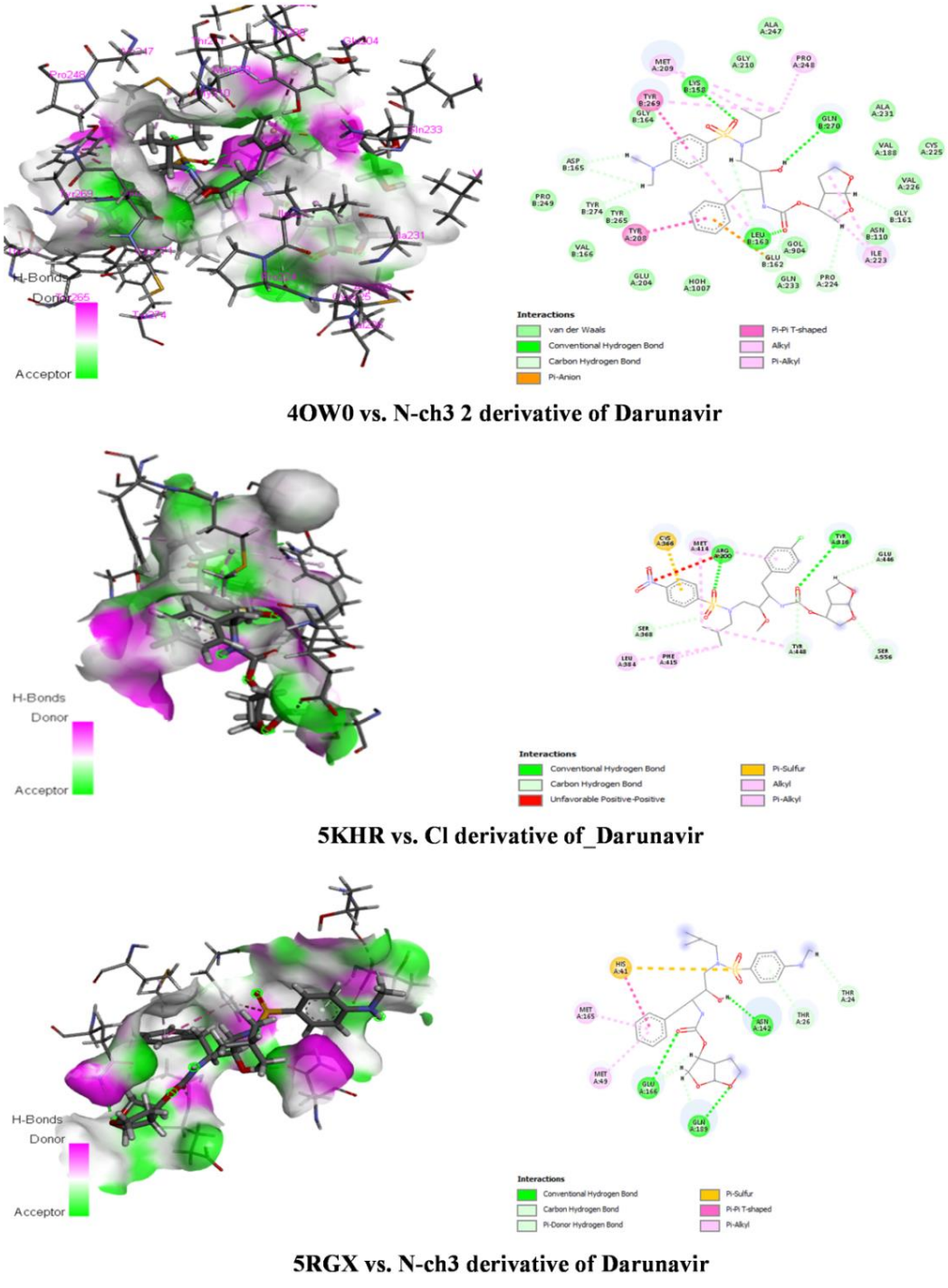

Figure 1. Binding patterns of darunavir derivatives.

The primary merits of this study stem from our findings, which indicate that the derivative substances might be used as therapeutical modalities against SARS-CoV-2. Furthermore, our findings will be useful for future in vitro and in vivo investigations using these modified compounds. However, in silico studies may fail to fully capture the intricate physiological conditions inherent in cellular systems. Thus, to confirm the validity and applicability of the present findings, it is imperative to conduct rigorous in vitro and in vivo experiments.

Conclusion

In general, our findings suggest that antivirals modification based on the functional group substitution using Cl, F, NCH_3, $N(CH3)_2$, OH^-, NH^{2-}, $HOOC^-$, or NO^- could improve the binding affinity against ACE2 receptor, Mpro, and RdRp. Therefore, the modified antivirals are potential in exerting anti-SARS-CoV-2 activities. The findings, however, were based on computational simulation and prediction which necessitate rigorous validation through the laboratory experiment. We encourage further experiments using in vivo and in vitro designs to identify novel candidate drugs and laying the groundwork for subsequent clinical trial applications focused on COVID-19 management.

Ethics approval

Not applicable.

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Competing interests

Authors declare no conflict of interest.

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Underlying data

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