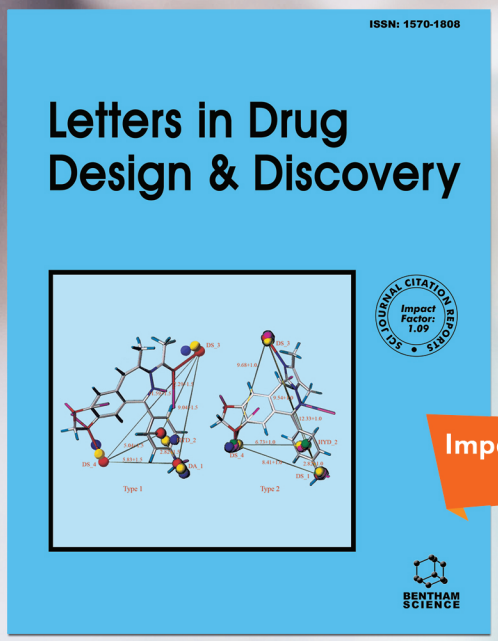
LETTERS ON DRUG DISCOVERY



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Letters in Drug Design & Discovery publishes letters, mini-reviews, highlights and guest edited thematic issues in all areas of rational drug design and discovery including medicinal chemistry, in-silico drug design, combinatorial chemistry, high-throughput screening, drug targets, and structure-activity relationships. The emphasis is on publishing quality papers very rapidly by taking full advantage of latest Internet technology for both submission and review of manuscripts. The online journal is an essential reading to all pharmaceutical scientists involved in research in drug design and discovery.

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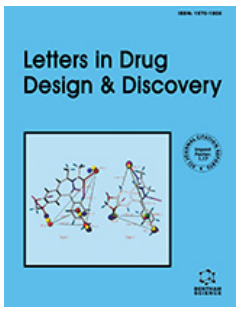

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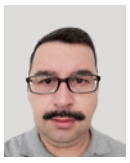

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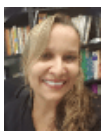

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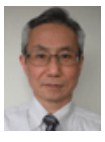

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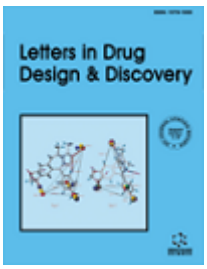

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RESEARCH ARTICLE

Molecular Docking Studies for Protein-Targeted Drug Development in SARS-CoV-2

Ahmad Dzulfikri Nurhan[1], Maria Apriliani Gani[1], Saipul Maulana[2], Siswandono Siswodihardjo[3], Chrismawan Ardianto[1] and Junaidi Khotib[1,*]

[1]*Department of Clinical Pharmacy, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia;* [2]*Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia;* [3]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia*

ARTICLE HISTORY

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Abstract: ***Background*:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic and emergency. Currently, there is no therapeutic agent that has been proven effective against the virus.

***Objective*:** We investigated and screened for 401 antiviral compounds that could inhibit one or more of the three protein targets in SARS-CoV-2 chymotrypsin-like (3CL) protease, RNA-dependent RNA polymerase, and spike glycoprotein) using the in-silico approach.

***Methods*:** Lipinski's rule of five was used as an initial screening for relevant compounds. Ligand preparation was conducted using JChem software and Schrödinger's LigPrep module, while protein elucidation was conducted using AutoDockTools-1.5.6. Molecular docking was analyzed using AutoDockVina.

***Results*:** Five antiviral compounds were obtained from each SARS-CoV-2 protein with ideal and potential binding energy as a candidate for target protein inhibition on SARS-CoV-2, TAK-981; lopinavir, mefloquine, and sitagliptin were potent inhibitors of 3CL protease; imatinib, relacatib, AZD7986, imatinib, and TAK-981 proteins showed potential as inhibitors of RdRp tetrandrine, and, selinexor, imatinib, lopinavir, and ciclesonide, showed potential as inhibitors of glycoprotein AZD7986. These compounds have better binding energy than the three comparator drugs, remdesivir, chloroquine, and hydroxychloroquine.

***Conclusion*:** We obtained several antiviral compounds with reliable binding energies to the SARS-CoV-2 proteins and potentially better efficacy than the three comparator drugs. Furthermore, this research will help accelerate the development of Covid-19 drugs.

Keywords: COVID-19, 3CL protease, RNA-dependent RNA polymerase, spike glycoprotein, AutoDock Vina, infectious disease.

1. INTRODUCTION

Over the last few decades, a substantial number of people worldwide have been affected by three epidemics caused by the coronavirus family, severe acute respiratory syndrome coronavirus (SARS-CoV; 2003), Middle East Respiratory Syndrome coronavirus (MERS-CoV; 2012), and SARS-CoV-2/coronavirus disease 2019 (COVID-19) [1]. The newest coronavirus, SARS-CoV-2, was first discovered on December 12, 2019, in Wuhan, Hubei Province, China [2]. By March 22, 2021, there were more than 122.5 million confirmed cases, with a mortality rate of more than 2.7 million (data obtained from the official website of the World Health Organization [WHO]) [3]. Although SARS-CoV-2 belongs to the genus Betacoronavirus, as do SARS-CoV and MERS-CoV, this new virus appears to be associated with milder infections. In terms of transmission, SARS and MERS generally spread through nosocomial infections. SARS-CoV-2 is much more prevalent through community transmission [1, 4], resulting in the faster spread of SARS-CoV-2 than SARS and MERS [5] and leading to WHO declaring SARS-CoV-2 pandemic a global emergency [6].

Currently, no vaccine or therapeutic agent is effective against the global SARS-CoV-2 pandemic [7]. Several studies confirmed that the SARS-CoV-2 genome possesses 14 open reading frames (ORFs) encoding 27 proteins [8, 9]. Chymotrypsin-like protease (3CL protease) is one of the translated non-structural proteins (NSPs) that plays an im-

*Address correspondence to this author at the Department of Clinical Pharmacy, Faculty of Pharmacy, Airlangga University, Post Code: 60155, Surabaya, Indonesia; Tel: +62-813-318-40710; Fax: +62-315-939-934;
E-mail: junaidi-k@ff.unair.ac.id.

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portant role in viral replication. It cleaves 11 sites in central and C-terminal polyprotein areas. In this regard, RNA-dependent RNA polymerase (RdRp) is responsible for the replication and transcription cycles of COVID-19 through its role in catalyzing the RNA synthesis of SARS-CoV-2 [10]. Therefore, drugs that can target these two proteins have the potential to be developed as a treatment against COVID-19 [8, 11]. Furthermore, spike glycoprotein, which is included in one of the translated structural proteins in SARS-CoV-2, functions as a major inducer of host immune responses. This spike protein mediates the invasion of SARS-CoV-2 on host cells by binding to a receptor protein called angiotensin-converting enzyme 2 (ACE2), located on the surface of the host cell membrane. Thus, the interaction of the compounds with these proteins in SARS-CoV-2 could lead to a potential inhibitory effect on the key proteins of SARS-CoV-2 and help identify a broad spectrum anti-SARS-CoV-2 medication [12-14].

Since discovering the first cases of COVID-19 infection in Wuhan, substantial efforts have been undertaken to search for and develop vaccines and therapeutic agents. Some studies suggested that remdesivir, chloroquine, and hydroxychloroquine could be developed as anti-COVID-19 therapy [15-17]. So far, remdesivir is promising because it exhibits broad-spectrum antiviral activity by inhibiting the viral RdRp (including SARS-CoV and MERS-CoV) [18]. Historically, chloroquine and hydroxychloroquine have been used as antimalarial and anti-autoimmune agents. A study revealed that chloroquine and hydroxychloroquine inhibit SARS-CoV-2 entry. They prevent viral cell fusion by interfering with ACE-2 receptor glycosylation and binding with spike proteins. Both drugs could be effective in the early stage of COVID-19 infection. Additionally, some evidence suggests that chloroquine and hydroxychloroquine can reduce cytokine storms [7, 18]. Notably, one of the primary causes of death in SARS-CoV-2 patients can be triggered by the emergence of a cytokine storm, contributing to acute respiratory distress [19].

Therefore, the investigation of antiviral compounds that can inhibit one or more of the three SARS-CoV-2 proteins (3CL protease, RdRp, and spike glycoprotein) is required to obtain potential compounds to overcome SARS-CoV-2. Additionally, this study seeks to identify compounds with lower binding energy than remdesivir, chloroquine, or hydroxychloroquine in those three proteins. This approach is important to predict each compound's inhibitory activity on the key proteins of SARS-CoV-2 to obtain potential drug candidates for development as an anti-COVID-19 treatment. This study adds to our knowledge of antiviral compounds that could be effective against SARS-CoV-2.

2. MATERIALS AND METHODS

2.1. Determination of Ligand Structure

In this study, we selected 401 antiviral compounds that have been approved as antiviral drugs or reported to have antiviral activity. On May 22, 2020, we found 401 antiviral compounds by searching http://pubchem.ncbi.nlm.nih.gov/ using the keyword "virus." Then, we screened the characteristics of the 401 antiviral compounds using Lipinski's rule of five, calculated by SWISSADME prediction (http://www.swissadme.ch/). Lipinski's rule of five was used for filtering because some compounds are still in the research and development stage (especially for compounds still being studied *in silico*, *in vitro*, and *in vivo*). Therefore, filtering using Lipinski's rule of five is intended to ensure that the compounds used in this study have drug-likeness properties. Furthermore, 258 compounds were obtained with characteristics that met Lipinski's rule of five [20]. Then, the ligand structure was formed using JChem software and optimized using Schrödinger's LigPrep module software. The atomic protonation was adjusted to pH 7 with Epic, and the geometry optimization used an OPLS_2005 force field.

2.2. Target Protein Elucidation

Three proteins were selected as docking targets: SARS-CoV-2 3 CL protease (PDB ID: 6M2N), (2) SARS-CoV-2 RNA-dependent RNA polymerase (Rpdp) (PDB ID: 6M71), and SARS-CoV-2 spike glycoprotein (PDB ID: 6VXX). The three-dimensional structure of the three proteins was downloaded from the Protein Data Bank (https://www.rcsb.org/), and it was saved in .pdb format. Furthermore, the protein was prepared by removing water molecules, adding hydrogen and Collman charge, and repairing the lost atoms. All of these processes were conducted using AutoDockTools-1.5.6 [21], and the prepared proteins were stored in pdbqt format.

2.3. Determination of Binding Sites and Molecular Docking

2.3.1. Determination of the Binding Site of the SARS-CoV-2 3CL Protease Protein

Of the three target proteins, 3CL protease protein was the only one with a complex with an inhibitor (co-crystal ligand). Binding sites were validated for 3CL protease protein by docking three times using AutoDockVina against the template ligand structure (co-crystal ligand) on the A chain of the 3CL protease protein. Then, the root mean square deviation (RMSD) was calculated by comparing these co-crystalline ligands before and after docking using PyMOL version 2.3.4. If the RMSD value was < 2, then the antiviral compound was classified in the good solution category, where the determination of the grid box to be used in the targeted docking could be based on the co-crystal ligand grid [22].

2.3.2. Determination of the Binding Site of the SARS-CoV-2 RdRp and Spike Glycoprotein

RdRp and spike glycoprotein are not complex inhibitors. Thus, we determined binding sites for RdRp protein (chain A) and spike glycoprotein (chain B) using blind docking against these two proteins using three comparator compounds: remdesivir, chloroquine, and hydroxychloroquine. The chains that were targeted for blind docking were selected based on chains that have pocket binding sites with high drug scores (top five) using DoGSiteScorer (http://dogsite.zbh.uni-hamburg.de) [23]. A drug score is a tendency for drugs to occupy a pocket binding site. It is reported as a ratio of 0–1, where higher the drug score, the higher the tendency for the drug to occupy a pocket binding

site. Blind docking was conducted three times using AutoDockVina by making a grid box that was sufficient to cover all sides of the protein so that the ligands were docked to all parts of the protein. Grid box selection for the targeted docking was determined based on the pocket binding sites with the lowest binding energy. The sites were consistently occupied by the three comparator compounds, remdesivir or chloroquine or hydroxychloroquine. Based on our findings, blind docking of comparator compounds (remdesivir, chloroquine, and hydroxychloroquine) was conducted on chain A of RdRp and chain B of spike glycoprotein.

2.3.3. Molecular Docking

Targeted docking was conducted on 258 compounds with characteristics that met Lipinski's rule of five against the selected grid boxes for the three proteins. As a comparator, this study used remdesivir, chloroquine, and hydroxychloroquine in all three proteins (SARS-CoV-2 3CL protease, RdRp, and spike glycoprotein). Additionally, specifically for the SARS-CoV-2 3CL protease protein, we used its co-crystalline ligand as a comparator. This protein already has a co-crystal ligand that acts as an inhibitor.

Molecular docking was performed using AutoDockVina docking software because it is relatively accurate and offers a shorter running time to predict ligand-protein interactions than the previously developed docking software AutoDock 4 [24]. This docking software is also free [25]. The hardware used for molecular docking was an ASUS X441U notebook with processor Intel® Core (TM) i3-6006U CPU @ 2.00GHz; 4.00 GB RAM; system type: 64-bit Operating System, x64-based processor; Microsoft Windows 10 Pro. The final docked structures were visualized using Discovery Studio Visualizer v17.2.016349.

3. RESULTS

3.1. Elucidation of Target Proteins and Determination of Binding Sites

3.1.1. Selected Binding Site of the SARS-CoV-2 3CL Protease

The results obtained from the 3 CL protease protein validation showed an RMSD value of 0.716 ± 0.006 Å (RMSD <2). Based on the RMSD value, the solution formed was categorized as a good solution. The SARS-CoV-2 3CL protease structure and its pocket binding sites are visualized in Fig. (**1**), and the selected grid boxes are presented in Table **1**.

3.1.2. Selected Binding Site of the SARS-CoV-2 RdRp and Spike Glycoprotein

At RdRp, the five pocket binding sites with the highest drug scores (0.85 ± 0.03) were located in chain A. However, three of the five pocket binding sites with the highest drug scores (*i.e.*, 0.87, 0.84, and 0.84) were in chain B in the spike glycoprotein.

Furthermore, the results obtained from blind docking showed that remdesivir consistently occupied a pocket binding site and had lower binding energies for the RdRp and spike glycoprotein than chloroquine and hydroxychloroquine. Therefore, the grid occupied by remdesivir was used as a grid box in the targeted docking of RdRp and spike glycoprotein. The structures of these two SARS-CoV-2 proteins (RdRp and spike glycoprotein) and their pocket binding sites are visualized in Fig. (**1**), and the selected grid boxes are presented in Table **1**.

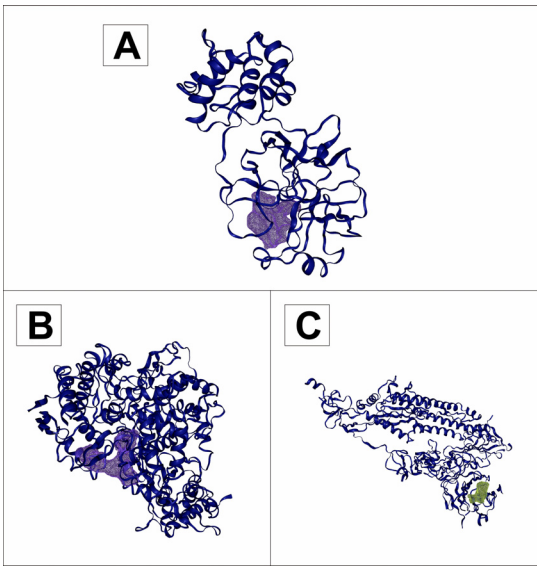

Fig. (1). Visualization of (**A**) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 3CL protease, (**B**) RNA-dependent RNA polymerase (RdRp), and (**C**) Spike glycoprotein with their binding sites and selected gridbox as a targeted docking; Notes: Proteins are represented by blue ribbons, and binding sites are indicated by purple for chymotrypsin-like (3CL) protease and RdRp protein and green for spike glycoprotein. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Selected grid boxes of three targeted proteins as a targeted docking.

Targeted Protein	Grid Box Size (Å); Centers (x, y, z)
3C-Like Protease (3CL Protease)	40, 40, 40; −32.981, −65.436, −41.404
RNA Dependent RNA Polymerase (RdRp)	40, 40, 40; 132.766, 112.761, 104.13
Spike Glycoprotein	40, 40, 40; 175.186, 176.76, 235.476

3.2. Binding of Comparator Compounds to SARS-CoV-2 3CL Protease, RdRp, and Spike Glycoprotein

The results of the docking analysis and final visualization of the docking results of the comparator compounds against the three SARS-CoV-2 proteins are presented in Figs. (**2**-**4**). The list of molecular interactions of each comparator compound against the three SARS-CoV-2 proteins is presented in Table **2**.

Table 2. Molecular interaction of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) comparators to three targeted proteins.

Comparator Compounds/Name	Molecular Interaction of Anti-SARS-CoV-2 Comparators to three Targeted Proteins		
	3CL Protease (PDB ID : 6M2N)	**RdRp (PDB ID : 6M71)**	**Spike Glycoprotein (PDB ID : 6VXX)**
Ligan co-chrystal (**5,6,7-trihydoxy-2-phenyl-4H-chromen-4-one)**	Cys145, His41, Glu166, Gly143, Met49, Cys44, and Asn142	N/A	N/A
Remdesivir	Cys145, His41, Glu166, Met49, Asn142, His164, and Arg188	Lys47, His133, Ser709, Asn781, Ser784, Thr710, Gly774, Lys780, Tyr129, Ala130, Asp135 and Cys139	Asn121, Asn188, His207, Phe192, Trp104, Ile203, Ile119, Phe194, Val126, Ile128, dan Val227
Chloroquine	His41, Met49, Cys44	Phe35, Val71, Arg33, and Tyr217	Asn121, His207, Val126
Hydroxychloroquine	Cys145, His41, Met49, Cys44, Asn142, His164, and Leu141	His133, Asn138	Phe192, Trp104, Ile203, Ile119, Phe194, Val126, Val227, dan Asp228

3.3. Binding of Antiviral Compounds to SARS-CoV-2 3CL Protease, RdRp, and Spike Glycoprotein

We downloaded 401 antiviral compounds from the PubChem database. Furthermore, we filtered the characteristics of these compounds using Lipinski's rule of five, and we obtained as many as 258 compounds. Then, we prepared these 258 compounds for docking analysis (see methods section). After the three SARS-CoV-2 proteins of 3CL protease, RdRp, and spike glycoprotein and the 258 compounds had been prepared. Docking analyses were performed using AutoDock Vina. The overall results of the docking analysis of 258 antiviral compounds are ordered based on the binding energy of the SARS-CoV-2 proteins of 3CL protease protein, RdRp, and spike glycoprotein. Furthermore, through these results, we classified antiviral compounds as potential inhibitors of each protein.

3.4. Potential Candidates for SARS-CoV-2 3CL Protease Inhibitors

Based on our docking analysis of 258 compounds that meet Lipinski's rule of five criteria, the 3CL protease protein found that 14 compounds had binding energy of less than or equal to the binding energy of the co-crystal ligand (≤ 7.8 kcal/mol). To further study the antiviral compounds that have high potential as SARS-CoV-2 3CL protease inhibitors, we decided to take the top five compounds (with the lowest binding energy) from the list of 14 compounds. The list of potential candidate compounds to be developed as SARS-CoV-2 3CL protease inhibitors are presented in Fig. (**2**). At the top of the list, there are two compounds (imatinib and TAK-981 [CID: 118628567]) that have the lowest binding energy (-8.6 kcal/mol) to this protein, and they can be assumed to have high potential as an inhibitor of 3CL protease. Imatinib forms several interactions with 3CL protease residues, including four interactions in the form of hydrogen bonds, namely with Cys145, Thr26, His41, and Asn142, and three hydrophobic interactions, which were with Cys44, Met49, and Met169. In TAK-981 (CID: 118628567), several interactions included seven interactions in the form of hydrogen bonds with Cys145, Ser144, Asn142, Glu166, Gln148, Met49, and Asp187, and three hydrophobic interactions with His41, His163, and Met165. The interactions between imatinib and TAK-981 against the 3CL protease protein make it a promising candidate for a 3CL protease inhibitor.

Next in rank were lopinavir, mefloquine, and sitagliptin, with binding energy values of −8.5, −8.3, and −8.3 kcal/mol. Lopinavir generated interactions in the form of hydrogen bonds with His41, Asn142, Cys145, Glu166, and Gln189 and hydrophobic interactions with Met49, Pro168, and Arg188. Mefloquine formed hydrogen bond interaction with Thr25, His41, Cys44, Asn142, and Cys145and hydrophobic interactions with Met49, His164, Met165, Asp187, and Arg188. Sitagliptin generated hydrogen bond interaction with His41, Glu166, and Asn142 and hydrophobic interactions with Met49, Cys145, Met165, Glu166, Asp187, and Arg188. The outcome of the investigation of the ligand-protein interactions on their docked form using Discovery Studio Visualizer v17.2.016349 is shown in Fig. (**2**).

3.5. Potential Candidates for SARS CoV-2 RdRp Inhibitors

In the SARS-CoV-2 RdRp protein, the results of docking analysis of the 258 compounds that met Lipinski's rule of five criteria showed that 22 compounds had binding energy of less than or equal to the binding energy of remdesivir (≤ -8.3 kcal/mol). To further explore candidate compounds with high potential to be developed as SARS-CoV-2 RdRp inhibitors, we selected five compounds with the lowest binding energy value from the list of 22 compounds (as shown in Table **S1**). Of the five potential compounds, the lowest binding energy value (−9.6 kcal/mol) occurred in tetrandrine. Moreover, tetrandrine showed several interactions with RdRp by generating interactions in hydrogen bonds with Ser709 and Asn781 and hydrophobic interactions with Tyr32, Lys47, and Asp135. The second and third ranks were occupied by relacatib and AZD7986 (CID: 118253852) with

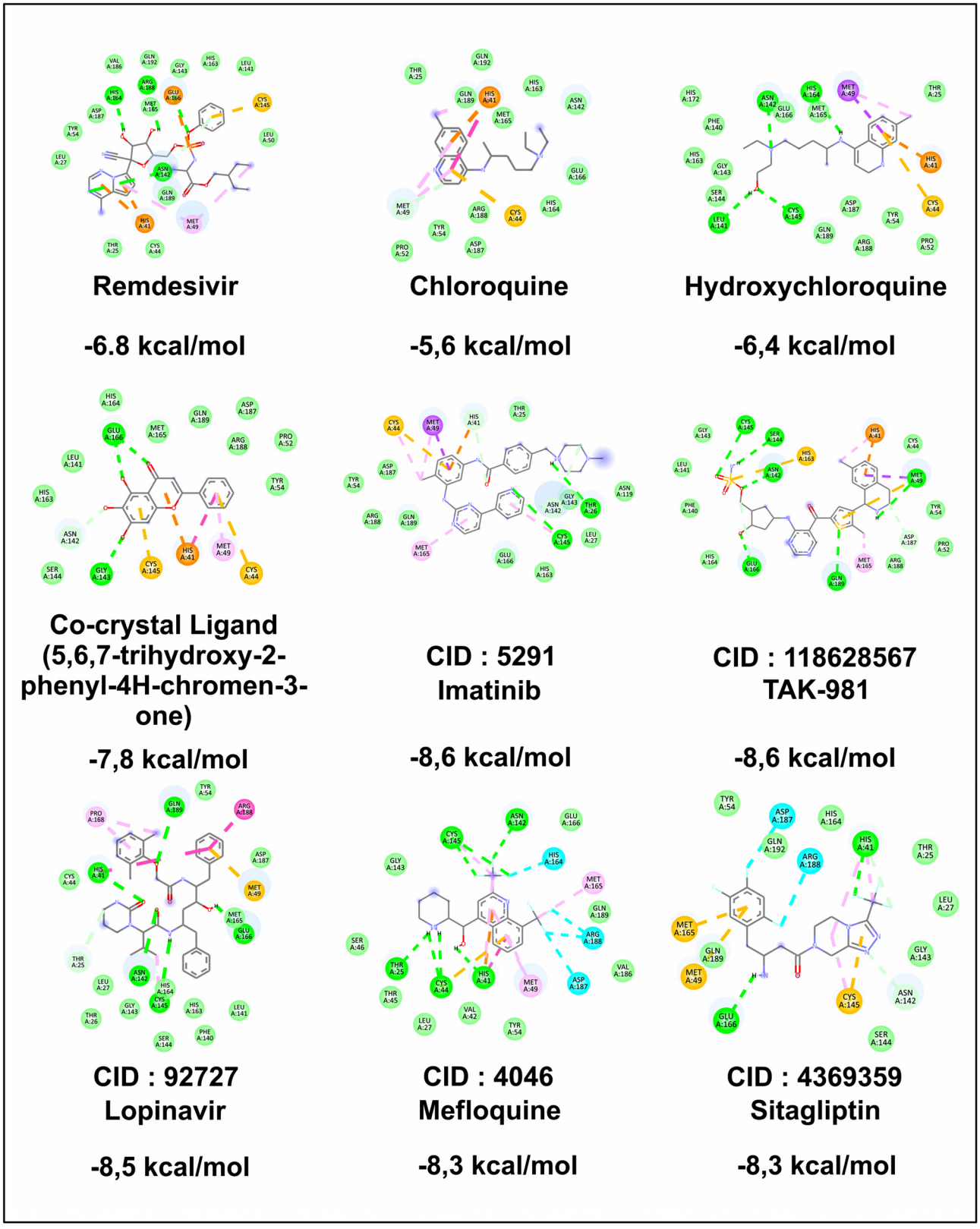

Fig. (2). Binding energy (kcal/mol) and molecular interaction of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) comparators and anti-SARS-CoV-2 potential candidates to the targeted protein SARS-CoV-2 chymotrypsin-like (3CL) protease. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

the same binding energy value of −9.0 kcal/mol. Relacatib interacted with RdRp by forming hydrogen bonds with Ser709, Asn781, Tyr129, His133, Asp140, Thr141, Cys139, and Asn138, as well as hydrophobic interactions with Lys47, Ala130, and Lys780, while AZD7986 (CID: 118253852) formed hydrogen bonds with Asp221, Asn209, and Asp218 and hydrophobic interactions with Arg33, Phe35, and Val71. Furthermore, the fourth and fifth ranks were held by two compounds with similar binding energy (−8.9 kcal/mol), imatinib and TAK-981 (CID: 118628567). In imatinib, we found hydrogen bonds with Ser709 and Tyr32 and hydrophobic interactions with Lys47, Asp140, Thr141, and Lys780. Additionally, in TAK-981 (CID: 118628567), we found hydrogen bonds with Ser709, His133, Lys47, Thr141, Asp140, Asn138, Cys139, and Ser784 as well as hydrophobic interactions with Lys780. Furthermore, the ligand-protein interactions on their docked form are visualized using Discovery Studio Visualizer v17.2.016349 are presented in Fig. (**3**).

3.6. Potential Candidates for SARS-CoV-2 Spike Glycoprotein Inhibitors

In the SARS-CoV-2 spike glycoprotein, the results of a docking analysis of 258 compounds that met Lipinski's rule of five criteria showed that 45 compounds had binding energy of less than or equal to the binding energy of remdesivir (≤ −7.2 kcal/mol). We also decided to select the five compounds with the lowest binding energies from 45 compounds for this protein. The list of potential inhibitor compounds for SARS-CoV-2 spike glycoprotein from our docking analysis is presented in Table **S2**. In this list, there are two potential compound candidates as spike glycoprotein inhibitors (*i.e*., AZD7986 [CID: 118253852] and selinexor), which are at the top of the list with the binding energy of −8.5 kcal/mol (Fig. **4**). AZD7986 (CID: 118253852) was found to form hydrogen bonds with Ser205 and Ser 207, as well as hydrophobic interactions, with Val126, Ile128, Phe168, Tyr170, Leu226, Val227, and Leu229, while selinexor formed hydrogen bonds with Asn121 and hydrophobic interactions with Phe192, Trp104, Phe194, Ile119, Ile203, Val126, Tyr170, Val227, and Leu229. The third rank of potential compound candidates as glycoprotein inhibitors is occupied by imatinib, with a binding energy of −8.4 kcal/mol. Imatinib formed hydrogen bond interactions with Asp228 and hydrophobic interactions with Val126, His207, Ile119, Ile203, Val227, Tyr170, and Leu226. Furthermore, the fourth rank was held by lopinavir (−8.2 kcal/mol), which formed hydrogen bonds with Arg190, Asn12, and His207 and hydrophobic interactions with Val126, Ile203, Ile119, Tyr170, Leu229, Val227, and Ile128. The last rank was occupied by Ciclesonide (−8.0 kcal/mol), which generated hydrophobic interactions with Val126, Leu226, His207, Phe192, and Tyr170. Visualization results and the list of further characteristics of these compounds are presented in Fig. (**4**).

4. DISCUSSION

Until now, the COVID-19 pandemic caused by SARS-CoV-2 has not subsided and is a global emergency. This has prompted many scientists and academics to research and develop effective drugs as therapy against COVID-19. In line with this, we conducted an *in silico* study of antiviral compounds that target three important proteins of SARS-CoV-2: 3CL protease, RdRp, and spike glycoprotein. Several studies confirm that 3CL protease (main protease) in coronavirus is essential for viral proteolytic maturation. It has been investigated as a potential target protein for preventing the spread of infection through the inhibition of viral polyprotein cleavage [26, 27]. We found several antiviral compounds that have the potential to be developed as SARS-CoV-2 3CL protease inhibitors. These compounds include imatinib, TAK-981 (CID: 118628567), lopinavir, mefloquine, and sitagliptin with binding energies of -8.6 to -8.3 kcal/mol (Fig. **2**).

Imatinib is widely recognized as an anticancer kinase-signaling inhibitor. Previous studies have shown anticoronal activity of imatinib in two types of coronaviruses, the SARS-CoV and MERS-CoV, especially in the early stages of infection after the internalization process. We revealed that imatinib inhibited the fusion of virions with the endosomal membrane, resulting in anticoronal activity [28]. Several clinical trials (NCT04346147, NCT04422678, NCT04394416, and NCT04356495) are also testing the potential of imatinib as a therapy against COVID-19. The findings from our *in silico* studies could complement the evidence regarding the potential efficacy of imatinib as a therapy against COVID-19, particularly regarding the possible interaction of imatinib with the key proteins of SARS-CoV-2 [29, 30]. Moreover, our findings are in line with the *in silico* study conducted by Nejat and Sadr (2020), which stated that imatinib is predicted to be useful in dealing with COVID-19 by reducing the virus affinity for ACE2, inhibiting the main protease and furin of SARS-CoV-2 and disrupting papain-like protease and p38MAPK functions [31]. Therefore, the development of further studies on imatinib is promising. TAK-981 (CID: 118628567) is the first drug intended as a selective SUMOylation inhibitor, with potential activity as an immune activator and showing antineoplastic activity. SUMOylation itself is known to have a key role in restraining type I interferon response [32, 33]. Currently, TAK-981 has been included in phase 1 and 2 clinical trials in patients with advanced or metastatic solid tumors or relapsed/refractory hematologic malignancies and a subset with COVID-19 (NCT number: NCT03648372). The previous study may be a compliment on the potential interaction of TAK-981 with the SARS-CoV-2 3CL protease. Lopinavir is an anti-human immunodeficiency virus (HIV) through its activity as an HIV protease inhibitor. The findings of our study were in line with the results of previous preclinical studies that showed that lopinavir had potential anti-coronavirus activity. Based on previous *in silico* studies, lopinavir might interact with the main protease SARS-CoV-2 [34, 35]. Other studies have also shown that early administration of lopinavir/ritonavir improves clinical outcomes of patients with mild to moderate disease. However, one study revealed that administering lopinavir/ritonavir was associated with higher rates of gastrointestinal side effects than standard care in patients with severe SARS-CoV-2 infection. Therefore, overall, the use of lopinavir in SARS-CoV-2 patients is still controversial and requires further confirmation [36-39]. Mefloquine is a drug approved as a therapy for malaria. A study by Dyall *et al*. [40] revealed that mefloquine

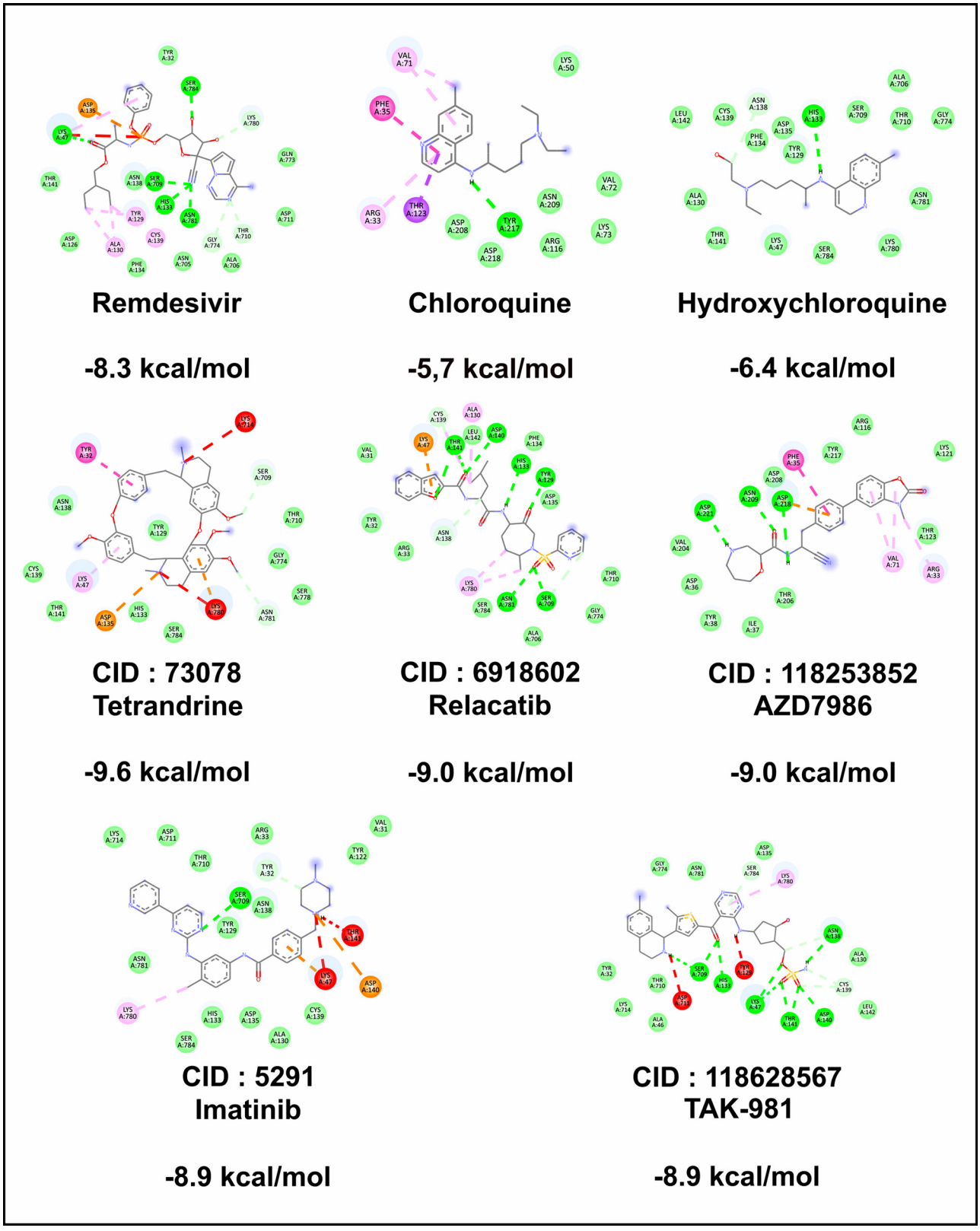

Fig. (3). Binding energy (kcal/mol) and molecular interaction of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) comparators and anti-SARS-CoV-2 potential candidates to the targeted protein SARS-CoV-2 RNA-dependent RNA polymerase. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

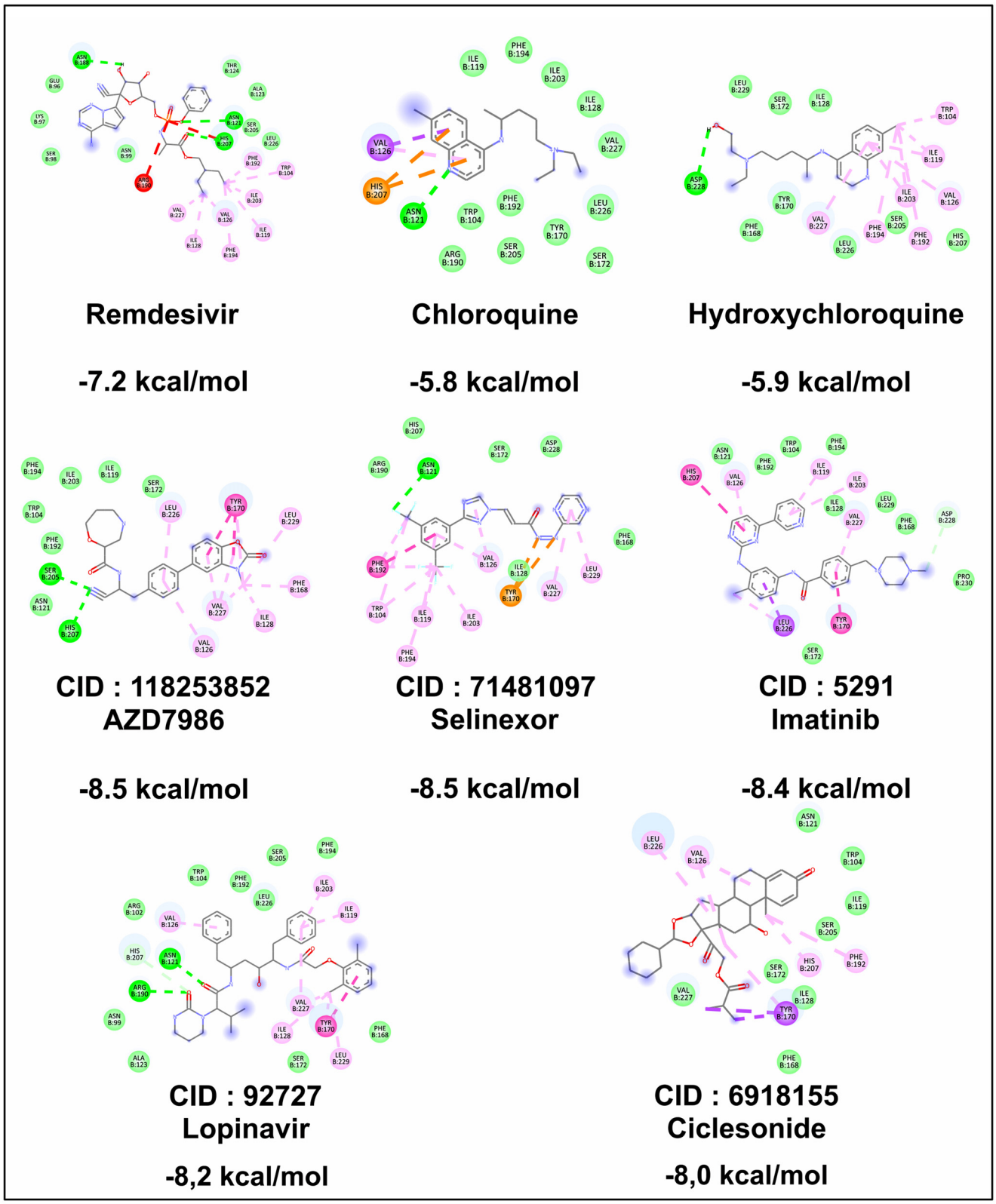

Fig. (4). Binding energy (kcal/mol) and molecular interaction of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) comparators and anti-SARS-CoV-2 potential candidates to the targeted protein SARS-CoV-2 spike glycoprotein. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

had antiviral activity against SARS-CoV and MERS-CoV. Based on previous *in silico* studies, halofantrine and mefloquine have the potential to inhibit the main protease of SARS-CoV-2 compared with other antimalarials [41]. Furthermore, our results are also in line with an *in vitro* study by Fan *et al*. [42], who found that mefloquine is effective in inhibiting COVID-19 replication. Furthermore, sitagliptin is also known as a DPP4-inhibitor class of antidiabetic drugs. So far, several assumptions and questions have emerged regarding the potential of the DPP4-inhibitor class of drugs in treating COVID-19 [43, 44]. Moreover, based on the study of Eleftheriou *et al*. (2020), sitagliptin has the potential to inhibit the main protease of SARS-CoV-2 with a binding energy of -8.80 kcal mol^{-1}, which agrees with our study [45]. Based on these findings and our study results, which showed that sitagliptin is a potentially effective compound against SARS-CoV-2, further study, and development of this group (especially sitagliptin) is promising.

The second target protein we used was SARS-CoV-2 RdRp. In general, viral replication in a host's cytoplasm depends on the function of RdRp. In particular, the key component of RdRp, also known as nsp12, plays a role in catalyzing the synthesis of viral RNA. Thus, this protein plays a central role in the replication and transcription cycle of the COVID-19 virus. Therefore, RdRp protein can be an important target in the development of anti-COVID-19 drugs [10, 46]. Using molecular docking, we obtained the following several compounds that were potential RdRp inhibitors: tetrandrine, relacatib, AZD7986 (Brensocatib; CID: 118253852), imatinib, and TAK-981. These compounds had binding energy against RdRp of -9.6 to -8.9 kcal/mol (Fig. **3**).

Tetrandrine remains at the experimental stage to be used as an anticancer, antimalarial, and antiparasitic agent. In terms of its potential as an anti-COVID-19 agent, our results were consistent with a recent *in silico* study by Singh and Florez [47], which showed that tetrandrine has low binding energy. Notably, tetrandrine is also being researched for its potential to fight COVID-19, and it has entered phase four clinical trials (NCT04308317). However, our results could help explore tetrandrine's benefits as an anti-COVID-19 agent, especially to determine its potential interaction of tetrandrine with the SARS-CoV-2 RdRp [48]. Relacatib is a potent cathepsin K inhibitor [49]. However, no research has revealed the potential of relacatib as an anti-COVID-19 agent. Our results suggest that further studies of relacatib are needed to confirm its potential as an anti-COVID-19 agent. AZD7986 (Brensocatib; CID: 118253852) is a reversible inhibitor of dipeptidyl peptidase I, which has been developed to treat patients with bronchiectasis. Dipeptidyl peptidase I is an enzyme responsible for activating neutrophil serine protease (NSP), such as neutrophil elastase, within neutrophils when formed in the bone marrow. Neutrophils play an important role in pathogen destruction and inflammation mediation [50]. The results of our study could provide a basis for further research on AZD7986 as a potential agent for COVID-19 treatment.

We used spike glycoprotein as the third target protein in this study. The spike consists of two functional subunits, which are responsible for binding to the host cell receptor (S1 subunit) and viral and cellular membrane fusion (S2 subunit). The process of coronavirus entry to host cells is through mediation by the spike's glycoprotein transmembrane that forms a homotrimer protruding from the surface of the virus [51, 52]. Therefore, it is very important to develop a potential agent as an inhibitor of this protein. Our study found that AZD7986 (Brensocatib; CID: 118253852), selinexor, imatinib, lopinavir, and ciclesonide were potential candidate compounds inhibitors of this protein. The binding energy formed by these compounds ranged from -8.5 to −8.0 kcal/mol (Fig. **4**).

Selinexor is a novel selective inhibitor of exportin 1, which is involved in the nuclear export of tumor suppressor proteins, and it is overexpressed in multiple myeloma. Based on the review by Bairi *et al*. (2020), selinexor has the potential to inhibit SARS-CoV-2 by inhibiting exportin 1, which is known to interact with several SARS-CoV-2 proteins [53]. Currently, selinexor is also being researched for its potential to fight COVID-19 and has completed a phase 2 clinical trial (NCT04349098). The data we have found may provide an overview of the potential interaction of selinexor with spike glycoprotein, which may have pharmacological activity as a therapy against COVID-19 [54, 55]. Ciclesonide is a safe drug, and it is widely used as an inhaled steroid for premature infants and can control chronic inflammation of the respiratory tract. Our study agrees with Sencanski *et al*. [56], who stated that ciclesonide has the potential to be a main protease inhibitor of SARS-CoV-2. They also found that this compound interacts with the main protease by binding to the allosteric domain [56]. Interestingly, ciclesonide showed suppression of SARS-CoV-2 replication in an *in vitro* study, although these findings were preliminary non-peer-reviewed data [57]. A case report on three cases of COVID-19 pneumonia also showed success with ciclesonide inhalation treatment [58]. However, further studies with a wider range of subjects are still needed to disclose the potential of ciclesonide as an anti-COVID-19 agent.

Although no effective drugs for SARS-CoV-2 are currently available, several studies have shown that remdesivir, chloroquine, and hydroxychloroquine might provide a good clinical response in SARS-CoV-2 patients [15, 17, 59]. Therefore, we used these three drugs as comparators in this study. The docking results of the three comparator compounds showed that remdesivir had low binding energy, particularly on the RdRp protein. This finding aligns with the postulate proposed that remdesivir is a potent inhibitor of RdRp [60]. Chloroquine and hydroxychloroquine showed considerably high binding energy on all three proteins. For this reason, it can be assumed that these two drugs may work through other mechanisms in the treatment of COVID-19.

Finally, we successfully conducted *in silico* studies of various antiviral compounds against the three key proteins of SARS-CoV-2. The application of the *in silico* method on this topic includes several advantages, such as an accelerated search for anti-SARS-CoV-2 candidates and its potential interaction with the key proteins of SARS-CoV-2, and it supports further studies of related compounds to overcome the COVID-19 pandemic. The study was also conducted with an affordable approach, minimizing the cost explosion due to the synthesis of chemical compounds and antiviral

testing against SARS-CoV-2. However, this study has several limitations. For example, the docking target pocket chosen may not reflect the functional role of proteins, even by selecting the binding pocket with the highest drug score. Another limitation of the study is that the physical movements of compounds in the targeted protein cannot be determined from the binding affinity value.

CONCLUSION

To overcome the emergency of the pandemic caused by COVID-19, studying and developing drugs that potentially act against COVID-19 is strategic. We have conducted drug discovery and drug repurposing strategies through an *in silico* study of antiviral compounds. Our study found that imatinib, tetrandrine, AZD7986, TAK-981, relacatib, selinexor, lopinavir, mefloquine, sitagliptin, and ciclesonide had good binding energies against at least one of the three proteins we targeted, 3CL protease, RdRp, and spike glycoprotein. Additionally, the binding energies of these compounds were better than the three comparator drugs, remdesivir, chloroquine, and hydroxychloroquine, which showed good potential for clinical response in SARS-CoV-2 patients in several studies. Therefore, the compounds we obtained in this study might have anti-COVID-19 activities. However, the results of this study require further confirmation, through *in vitro*, *in vivo*, and clinical trials, before they can be widely applied.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data presented in our manuscript entitled “Molecular Docking Studies for Protein-Targeted Drug Development in SARS-CoV-2” is complete. In addition, with this response, we also include a document “Supplementary Material,” which can be published together with our manuscript and support our study's findings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher’s website along with the published article.

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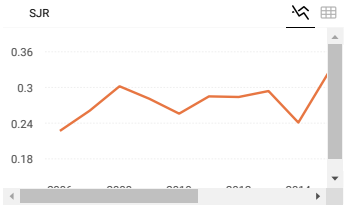

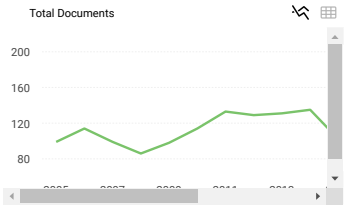

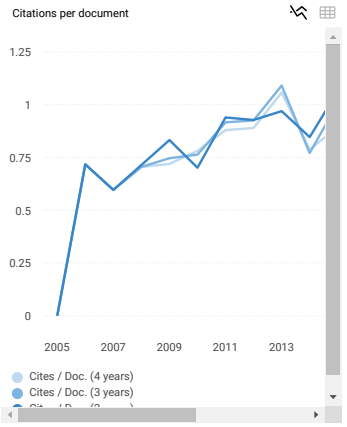

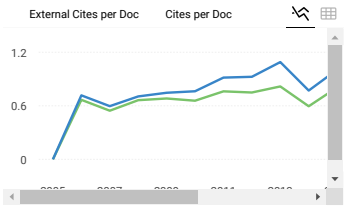

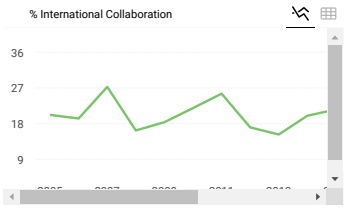

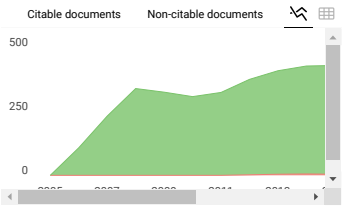

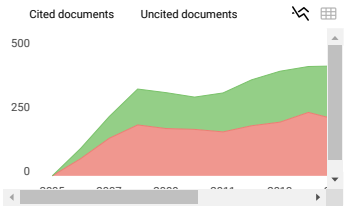

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