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Computational modeling of the pharmacological actions of some antiviral agents against SARS-CoV-2

Abayomi Emmanuel Adegboyega[1,2], Titilayo Omolara Johnson[1,3], Simeon Omale[2,4]

[1]DEPARTMENT OF BIOCHEMISTRY, FACULTY OF MEDICAL SCIENCES, UNIVERSITY OF JOS, JOS, PLATEAU, NIGERIA; [2]AFRICA CENTRE OF EXCELLENCE IN PHYTOMEDICINE RESEARCH AND DEVELOPMENT, UNIVERSITY OF JOS, JOS, PLATEAU, NIGERIA; [3]DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PURE AND APPLIED SCIENCES, LANDMARK UNIVERSITY, OMUARAN, KWARA, NIGERIA; [4]DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY, FACULTY OF PHARMACEUTICAL SCIENCES, UNIVERSITY OF JOS, JOS, PLATEAU, NIGERIA

1. Introduction

Coronaviruses (CoVs) are a family of viruses that cause respiratory illnesses ranging from the common cold to severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) [1]. CoVs have caused a major outbreak of human fatal pneumonia since the beginning of the 21st century. SARS-associated Coronavirus (SARS-CoV) broke out in 2003 and MERS-associated Coronavirus (MERS-CoV) in 2012 with a lethal rate of 10% and a fatality rate of 35%, respectively [2]. Toward the end of 2019, a novel coronavirus known as 2019 novel coronavirus (2019-nCoV) or SARS-associated coronavirus 2 (SARS-CoV-2) closely related to SARS-CoV was identified as the causative agent of the virulent disease called coronavirus disease 2019 (COVID-19). The disease, which was said to originate from Wuhan, Hubei province of China, is spreading rapidly across the globe with human-human transmission [3,4].

SARS-CoV-2 belongs to the genus *Betacoronavirus* along with MERS-CoV [5,6] and causes COVID-19 with common respiratory symptoms, as well as fever, cough, shortness of breath, dyspnea, and in more severe cases, pneumonia, SARS, kidney failure, and even death [2]. Currently, there is no food and drug administration—approved vaccine and/or drug treatment against the new coronavirus (SARS-CoV-2). Hence, identifying effective antiviral agents to combat the disease is urgently needed because of the pandemic [6]. Some known antiviral agents which include remdesivir, ritonavir, chloroquine, lopinavir, and dieckol [4,6–9] have been suggested to have inhibitory activity against the virus but their mode of action, pharmacokinetics, and pharmacodynamics are uncertain.

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Several computational modeling methods are available to determine these pharmacological actions of a drug. For a molecule to be effective as drug, it must reach its biological target in a sufficient bioactive form, form complex with the target, and then elicit its biological effect. These factors are determined by the molecule's rate of absorption, distribution, metabolism, and excretion (ADME) in the body. SwissADME web tool gives optimal prediction of these parameters, while molecular docking model predicts the binding affinity and molecular interaction of the molecule with its biological target [10]. The toxicity of a molecule in the biological system is also an essential factor in drug design, PROTOX-II webserver provides a free access for in silico toxicity predictions of the chemical [11].

CoVs contain some critical proteins that are been considered as therapeutic targets against SARS-CoV-2. These include: Spike (S) protein, Papain-like protease (PLpro), 3-chymotrypsin-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), and main protease [2]. The spike (S) protein facilitates viral entry into target cells. Entry depends on binding of the surface unit, S1, of the S protein to a cellular receptor, angiotensin-converting enzyme 2 (ACE2), which facilitates viral attachment to the surface of target cells. The priming of S protein by cellular proteases (serine protease TMPRSS2) entails S protein cleavage at the S1/S2, thus facilitating fusion of viral and cellular membranes, a process driven by the S2 subunit [12]. PLpro and 3CLpro are the two major proteases essential for coronaviral replication [13]. Coronavirus PLpro is known to process the viral polypeptide onto functional proteins and also dampen host antiviral response by taking over the ubiquitin (Ub) system. SARS-3CLpro is a cysteine protease indispensable to the viral life cycle [3]. RdRp of coronavirus catalyzes the replication of RNA from RNA templates, hence it is an indispensable enzyme in the viral replication [14]. Coronavirus main protease is an essential enzyme responsible for the processing of the polyproteins that are translated from the viral RNA [15]. Molecular interactions of a drug with these proteins leading to their inhibition could lead to a therapeutic intervention against SARS-CoV-2, and this can be predicted using molecular docking analysis.

This study aims to evaluate and compare the pharmacological actions and toxicological potential of the five antiviral agents: remdesivir, ritonavir, chloroquine, lopinavir, dieckol, and their structurally related compounds through in silico molecular docking against SARS-CoV-2 target proteins, ADME, and PROTOX-II testing.

2. Material and methods

2.1 Proteins and ligands collection

Five antiviral drugs with reported inhibitory activity against SAR-CoV-2: ritonavir, remdesivir, chloroquine, lopinavir, dieckol [5,12,14–16], and their structurally similar zinc-lead compounds (five for each) were subjected to molecular docking analysis against five SARS-CoV-2 target proteins: spike (S) protein (Spro; 6LZG), PLpro; 6W9C, 3CLpro; 6LU7, main protease (Mpro; 6W63), and RdRp; 6M71. The crystal structures of

SARS-CoV-2 target proteins were gotten from the protein data bank (PDB) and the structure data file format or canonical smiles of the test compounds were obtained from the PubChem database and then converted to PDB format using UCSF Chimera 1.14. AutoDock 4.2 was used to prepare PDBQT format files for target and ligand docking. Molecular docking was performed using AutoDock vina in PyRx and finally, the results were analyzed using UCSF Chimera 1.14 and Discovery Studio 2020 [3,17,18].

2.2 Absorption, distribution, metabolism, excretion, and toxicity screening

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the antiviral drugs and their structurally related lead compounds were determined using an in silico integrative model predicted at the SwissADME and PROTOX-II web servers, respectively. Using a huge database, the servers speculate physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug-likeness, medicinal properties, and toxicity of compounds with high precision [19].

2.3 Virtual screening

A library of ligands (the five antiviral drugs and their structurally similar lead compounds) was created from PubChem and SwissSimilarity database, respectively. The candidates in the obtained library were subjected to molecular docking using AutoDock Vina program in PyRX software. The ligands with high-docking score were filtered by Lipinski's rule and by their SwissADME physicochemical properties. Only the molecules which following Lipinski's rule and SwissADME predictions can be considered as hits were subjected to post-docking analysis using Discovery Studio 2020 and UCSF Chimera 1.14, and toxicity screening using PROTOX-II web server. Top-ranked candidates were suggested for experimental screening as potential therapeutic agents for the treatment of SARS-CoV-2 [18].

2.4 Statistical analysis

Statistical analysis was performed by one-way ANOVA using GraphPad Prism 8.02, and the results were expressed as mean ± SEM. Group differences were determined by Tukey's multiple comparison test ($P < .05$).

3. Results

3.1 Binding affinity of the antiviral drugs and their derivatives with SARS-CoV-2 target proteins

The docking scores (kcal/mol) of the five known antiviral drugs and structurally related zinc lead-like compounds show that dieckol exhibited the highest binding affinity with

all target proteins (3CLpro = −9.3 kcal/mol; Spro B = −8.5 kcal/mol; Spro AB = −10.3 kcal/mol; RdRp = −9.3 kcal/mol; PLpro = −9.6 kcal/mol; Mpro = −9.2 kcal/mol). Lopinavir showed the second-highest binding affinity with 3CLpro. GS-6620, a remdesivir derivative binds with Spro AB (−8.4 kcal/mol). ZINC82312351 and ZINC95451461 gave the same binding energy with Spro B (−7.1 kcal/mol). Remdesivir, Ritonavir, and WD5DUG7X38 also showed the same binding energy RdRp (−7.5 kcal/mol). ZINC82312352 gave the second-highest binding affinity with PLpro (−7.9 kcal/mol), while Lopinavir and Ritonavir bind with Mpro with the same binding energy (−8.2 kcal/mol) (Table 25.1).

The comparative and statistical analysis of the docking scores of the five antiviral drugs shows that the binding energy of the inhibitors fitness with the binding site of all target proteins is as follows: dieckol > lopinavir > remdesivir > ritonavir > chloroquine. Data expressed as Mean ± SD (Table 25.2 and Fig. 25.1).

The statistical comparison and ranking of the first 14 compound with highest binding energy with all target SARS-CoV-2 proteins showed that dieckol, CHEMBL3120784, Lopinavir, WD5DUG7X38, and ZINC82312352 were ranked the first five compounds with highest binding affinity. The average binding affinity of dieckol with all target proteins was significantly higher ($P < .05$) when compared with other ligands (Fig. 25.2).

3.2 Absorption, distribution, metabolism, excretion, and toxicity predictions

SwissADME predicted values of pharmacokinetics, pharmacodynamics, and drug-likeness of the 14 selected compounds showed that most of the compounds fulfilled the important criteria for drug-likeness and optimal toxicity as obtained from SwissADME screening. The result showed that the compounds relatively fulfilled the Lipinski rule of 5, have moderate water solubility, gastrointestinal absorption (GI) absorption, bioavailability, synthetic accessibility, and optimum lipophilicity as expressed in Tables 25.3 and 25.4, respectively. Considering all the models for water solubility: ESOL Log S, Ali Log S, Silicos-IT LogSw, we can infer that most of the selected compounds are moderately water-soluble.

3.3 Toxicity profile of potential SARS-CoV-2 inhibitors

The PROTOX-II predicted toxicity profile of the selected compounds showed that the majority of the compounds demonstrated no toxic effects against drug toxicity targets and toxicological pathways. Although Lopinavir was predicted to have slight toxic effects against mitochondrial membrane potential, dieckol with aryl hydrocarbon receptor (AhR), while ZINC82312352 and ZINC82312351 may exhibit AhR, estrogen receptor alpha, estrogen receptor ligand binding domain, mitochondrial membrane potential, and phosphoprotein (tumor suppressor) p53 toxicity (Table 25.5).

Table 25.1 Docking scores (kcal/mol) of five known antiviral drugs and their derivatives.

Ligands	3CLpro	Spro AB	Spro B	RdRp	PLpro	MPro
CHEMBL3120784	−7.8	−8.5	−6.6	−7.4	−7.4	−8
CHEMBL4068210	−6.3	−7.8	−6.1	−6.5	−5.8	−7.1
Chloroquine	−5.4	−6.2	−5.2	−5.7	−4.9	−5.4
Dieckol	−9.3	−10.3	−8.5	−9.3	−9.6	−9.2
GS-6620	−6.7	−8.4	−6.1	−7.4	−7	−8
Lopinavir	−8.8	−8.1	−6.4	−7.2	−6.6	−8.2
Remdesivir	−6.4	−7.7	−6.5	−7.5	−6	−8.1
Ritonavir	−6.7	−7.8	−5.8	−7.5	−5.2	−8.2
SCHEMBL10142598	−7	−8.1	−6.3	−7.3	−6.6	−7.8
WD5DUG7X38	−7.5	−8.1	−6.4	−7.5	−6.9	−7.8
ZINC01729567	−5	−5.9	−4.8	−5.7	−5	−5.1
ZINC03335389	−6.5	−7.1	−6.2	−5.9	−6.5	−6.5
ZINC05890446	−6.2	−6.6	−6.4	−6.3	−6.8	−6.2
ZINC0602572	−5.8	−6	−5.3	−5.5	−5.2	−5.3
ZINC06036375	−5.6	−6.2	−5.2	−5.5	−5.2	−5.5
ZINC19221342	−5.6	−5.7	−4.9	−5.7	−6.3	−5.6
ZINC40116433	−6.6	−7.6	−6.2	−6.9	−6.6	−7.4
ZINC40116435	−6.6	−7.4	−6.4	−7.1	−6.2	−7
ZINC60802547	−6.7	−7.6	−6.4	−6.4	−6.3	−6.7
ZINC71904549	−7.1	−7.4	−6.1	−6.4	−6.4	−7.3
ZINC72271523	−5.8	−6.6	−5.6	−6.4	−6.2	−6.3
ZINC76422110	−6.9	−7.7	−6	−6.1	−6.9	−7.2
ZINC82312351	−7.6	−7.1	−7.1	−6.4	−6.5	−7.3
ZINC82312352	−7.7	−7.6	−6.8	−6.3	−7.9	−7.3
ZINC82312353	−6.3	−6.8	−5.9	−6.5	−6.5	−6.9
ZINC82312354	−6.9	−6.7	−6.2	−6.4	−6.4	−7.1
ZINC95451460	−6.5	−7.4	−6.8	−6.6	−7.1	−6.6
ZINC95451461	−6.5	−7.3	−7.1	−6.9	−6.8	−7
ZINC97568921	−7.1	−7.9	−6.8	−6.9	−6.9	−7.7
ZINC97568922	−7	−7.8	−6.7	−6.8	−6.7	−7.2

3CLpro, 3-Chymotrypsin-like protease; *Mpro*, main protease; *PLpro*, Papain-like protease; *RdRp*, RNA-dependent RNA polymerase; *Spro AB*, Spike (S) protein complex with ACE2; *Spro B*, Spike (S) protein.

Table 25.2 Comparative docking scores (kcal/mol) of five antiviral drugs against SARS-CoV-2 target proteins.

Drugs/Proteins	Spro B	3CLpro	Spro AB	RdRp	Plpro	Mpro
Ritonavir	−5.8	−6.7	−5.8	−7.5	−5.2	−8.2
Remdessivir	−6.5	−6.4	−6.5	−7.5	−6	−8.1
Chloroquine	−5.2	−5.4	−5.2	−5.7	−4.9	−5.4
Lopinavir	−6.4	−8.8	−8.1	−7.2	−6.6	−8.2
Dieckol	−8.5	−9.3	−10.3	−9.3	−9.6	−9.2

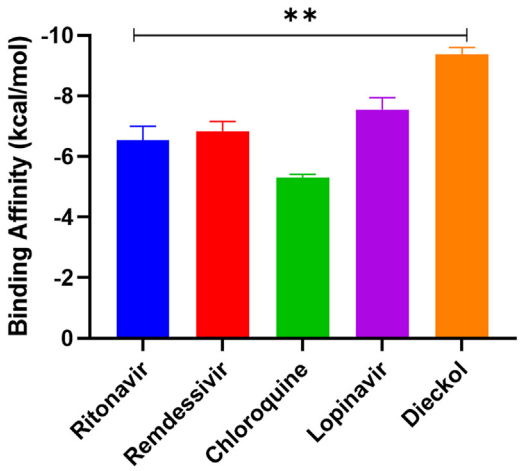

FIGURE 25.1 The binding affinity of known Antiviral drugs with SARS-CoV-2 target proteins (3CLpro, Spro B, Spro AB, RdRp, PLpro, Mpro).

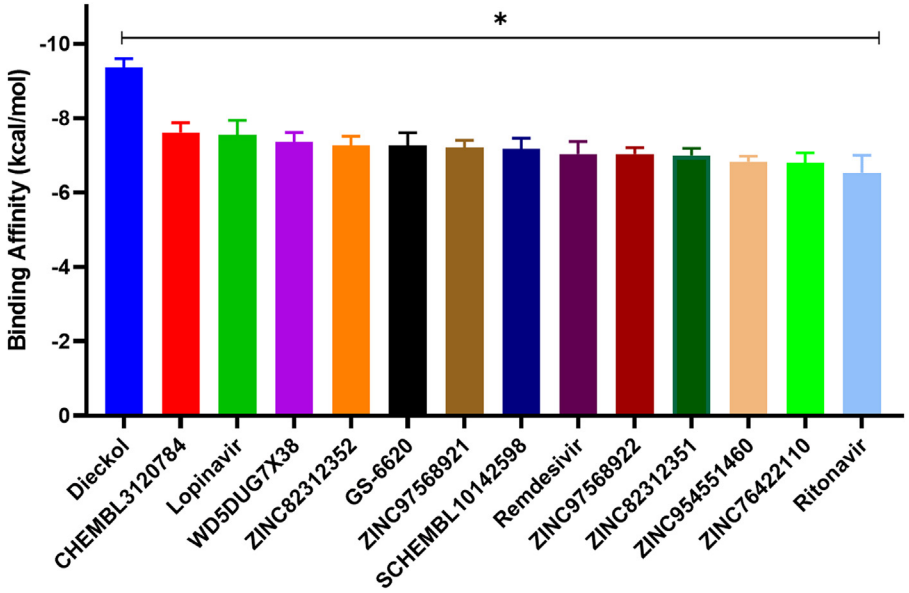

FIGURE 25.2 Ranks of Ligands with the highest binding affinity against all SARS-CoV-2 target proteins (Mpro, 3CLpro, Spro, RdRp, PLpro).

Aryl hydrocarbon Receptor (AhR), Androgen Receptor (AR), Androgen Receptor Ligand Binding Domain (AR-LBD), Estrogen Receptor Alpha (ER), Estrogen Receptor Ligand Binding Domain (ER-LBD), Peroxisome Proliferator-Activated Receptor Gamma (PPAR-Gamma), Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE), Heat shock factor response element (HSE), Mitochondrial Membrane Potential (MMP), Phosphoprotein (Tumor Suppressor) p53, ATPase family AAA domain-containing protein 5 (ATAD5).

Table 25.3 SwissADME predicted values of pharmacokinetics, pharmacodynamics, and drug-likeness of selected ligands with a high-binding affinity toward target proteins of SARS-CoV-2.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
ESOL Log S	−7.61	−6.64	−6.99	−4.12	−3.49	−2.8	−2.8	−4.72	−4.72	−4.32	−2.43	−2.54	−3.85	−2.43
Ali Log S	−10.63	−8.21	−10.08	−6.01	−4.91	−3.6	−3.6	−6.72	−6.72	−6.21	−2.51	−3.51	−4.64	−2.51
Silicos-IT LogSw	−6.32	−10.05	−10.02	−4.77	−4.2	−1.79	−1.79	−5.19	−5.19	−5.35	−3.83	−4.07	−6.15	−3.83
Gastrointestinal absorption	Low	High	Low	Low	Low	High	High	Low	Low	Low	High	High	High	High
BBB permeant	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Pgp substrate	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Log Kp (cm/s)	−7.37	−5.93	−6.4	−8.62	−9.2	−6.64	−6.64	−8.48	−8.48	−8.57	−7.55	−7.36	−6.22	−7.55
Lipinski violations	3	1	2	2	2	0	0	2	2	2	0	0	0	0
Bioavailability score	0.17	0.55	0.17	0.17	0.17	0.55	0.55	0.17	0.17	0.17	0.55	0.55	0.55	0.55
Synthetic accessibility	4.68	5.67	6.45	6.33	6.08	2.19	2.19	6.54	6.54	6.45	3.25	3.05	3.41	3.25

A, Dieckol; *B*, Lopinavir; *C*, Ritonavir; *D*, Remdesivir; *E*, CHEMBL3120784; *F*, ZINC82312352; *G*, ZINC82312351; *H*, WD5DUG7X38; *I*, GS-6620; *J*, SCHEMBL10142598; *K*, ZINC97568921; *L*, ZINC95451460; *M*, ZINC76422110; *N*, ZINC97568922.

Table 25.4 SwissADME predicted lipophilicity (Log P) values of selected ligands with high docking scores against target proteins of SARS-CoV-2.

Molecules	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P	Mean Log P
Dieckol	2.66	4.87	7.62	0.04	1.75	3.388
Lopinavir	3.44	5.92	3.57	2.93	6.02	4.376
Ritonavir	4.42	6.05	5.6	1.8	7.33	5.04
Remdesivir	3.24	1.91	2.21	0.18	−0.05	1.498
CHEMBL3120784	3.27	0.85	1.57	−0.22	−0.76	0.942
ZINC82312352	1.87	1.67	2.01	0.38	0.59	1.304
ZINC82312351	1.27	1.67	2.01	0.38	0.59	1.184
WD5DUG7X38	3.66	2.47	2.78	0.58	0.43	1.984
GS-6620	3.66	2.47	2.78	0.58	0.43	1.984
SCHEMBL10142598	4.48	2.1	2.6	0.38	0.48	2.008
ZINC97568921	2.23	1.08	−0.32	0.89	1.31	1.038
ZINC95451460	2.35	1.51	1.04	0.81	1.51	1.444
ZINC76422110	3.13	3.07	2.24	1.55	4.41	2.88
ZINC97568922	2.3	1.08	−0.32	0.89	1.31	1.052

Log Po/w values for most of the selected compounds expressed in Table 25.4 were found to be positive. These positive values signify that all the molecules are optimally lipophilic and fulfill the essential criteria for drug molecules, Log P < 5 [17].

Table 25.5 PROTOX-II toxicity profile predictions of the selected compounds.

Target	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Hepatotoxicity	−	−	+	−	−	−	−	−	−	−	−	−	−	−
Carcinogenicity	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Immunotoxicity	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Mutagenicity	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Cytotoxicity	−	−	−	−	−	−	−	−	−	−	−	−	−	−
(AhR)	+	−	−	−	−	+	+	−	−	−	−	−	−	−
(AR)	−	−	−	−	−	−	−	−	−	−	−	−	−	−
(AR-LBD)	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Aromatase	−	−	−	−	−	+	+	−	−	−	−	−	−	−
(ER)	−	−	−	−	−	+	+	−	−	−	−	−	−	−
(ER-LBD)	−	−	−	−	−	+	+	−	−	−	−	−	−	−
(PPAR-Gamma)	−	−	−	−	−	−	−	−	−	−	−	−	−	−
(nrf2/ARE)	−	−	−	−	−	−	−	−	−	−	−	−	−	−
(HSE)	−	−	−	−	−	−	−	−	−	−	−	−	−	−
(MMP)	+	+	−	−	−	+	+	−	−	−	−	−	−	−
p53	−	−	−	−	−	+	+	−	−	−	−	−	−	−
(ATAD5)	−	−	−	−	−	−	−	−	−	−	−	−	−	−

Active = (+); Inactive = (−). *A*, Dieckol; *B*, Lopinavir; *C*, Ritonavir; *D*, Remdesivir; *E*, CHEMBL3120784; *F*, ZINC82312352; *G*, ZINC82312351; *H*, WD5DUG7X38; *I*, GS-6620; *J*, SCHEMBL10142598; *K*, ZINC97568921; *L*, ZINC95451460; *M*, ZINC76422110; *N*, ZINC97568922.

3.4 Molecular docking interactions

Figs. 25.3–25.9 shows the molecular docking interactions of some selected compounds with a high-binding affinity toward corresponding target proteins of SARS-CoV-2. The molecular mechanism calculations showed that dieckol binds to 3CLpro of SARS-CoV-2 with at least eight conventional hydrogen bonds among others, which may likely be the reason while it has the highest binding affinity with 3CLpro among all the compounds screened (Fig. 25.3). However, molecular complexation of lopinavir with the 3-CLpro involved the following bonds: van der Waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Donor Hydrogen Bond, Pi-Pi Stacked, Pi-Pi T-Stacked, Amide-Pi Stacked, Alkyl and Pi-Alkyl Bond (Fig. 25.4). Furthermore, van der Waals force, Conventional Hydrogen Bond, Pi-Cation bond among others were observed to facilitate the complexation of dieckol and its derivative ZINC82312352 with PLpro of SARS-CoV-2. Although ZINC82312352 binding pocket is different from that of dieckol (Figs. 25.5 and 25.6). Fig. 25.7 shows the complexation of dieckol, lopinavir, remdesivir derivatives: CHEMBL3120784, GS-6620, SCHEMBL10142598, and WD5DUG7X38 at the binding pocket of ACE2 complex with Spike protein. The molecular docking interactions showed that all the ligands favorably bind to the same binding pocket of ACE2 as against the viral spike protein. However, the molecular docking of all the ligands with Spike (S) protein without ACE2 complex showed that dieckol form complex with the viral spike protein through van der Waals force, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Donor Hydrogen Bond, Pi-Pi T-shaped and Pi-Alkyl bond (Fig. 25.8). Also, the molecular interactions of selected compounds with RdRp of SARS-CoV-2 showed that all the ligands bind fitly to the same binding site of the enzyme with dieckol having the strongest complexation bonds (Fig. 25.9).

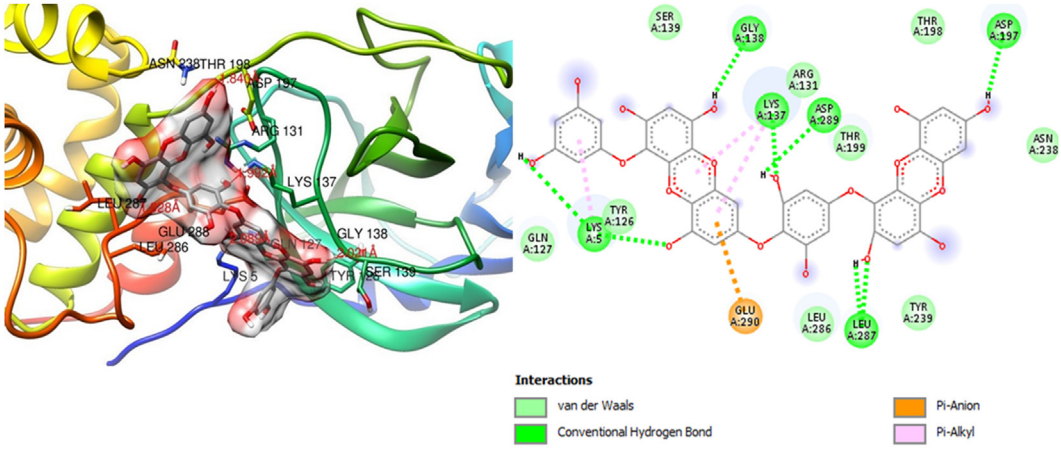

FIGURE 25.3 Molecular interactions of Dieckol with 3-Chymotrypsin-like protease of SARS-CoV-2. Three-dimensional left—ligand in the binding site of the target proteins; Two-dimensional right—ligand interactions with the amino acid residues of the SARS-CoV-2 target proteins binding site.

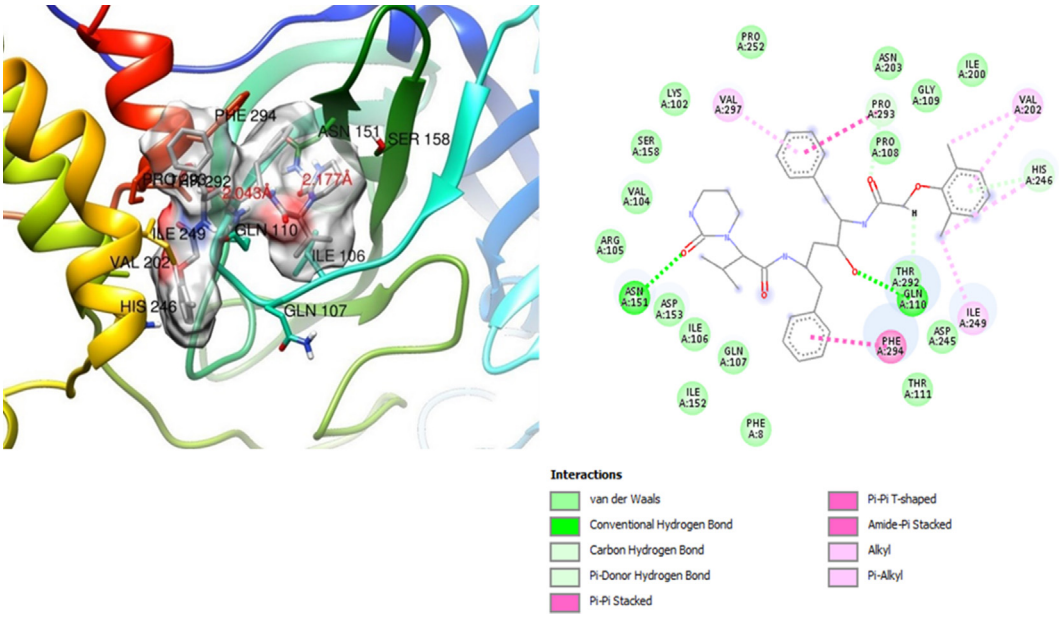

FIGURE 25.4 Molecular interactions of Lopinavir with 3-Chymotrypsin-like protease of SARS-CoV-2. Three-dimensional left—ligand in the binding site of the target proteins; Two-dimensional right—ligand interactions with the amino acid residues of the SARS-CoV-2 target proteins binding site.

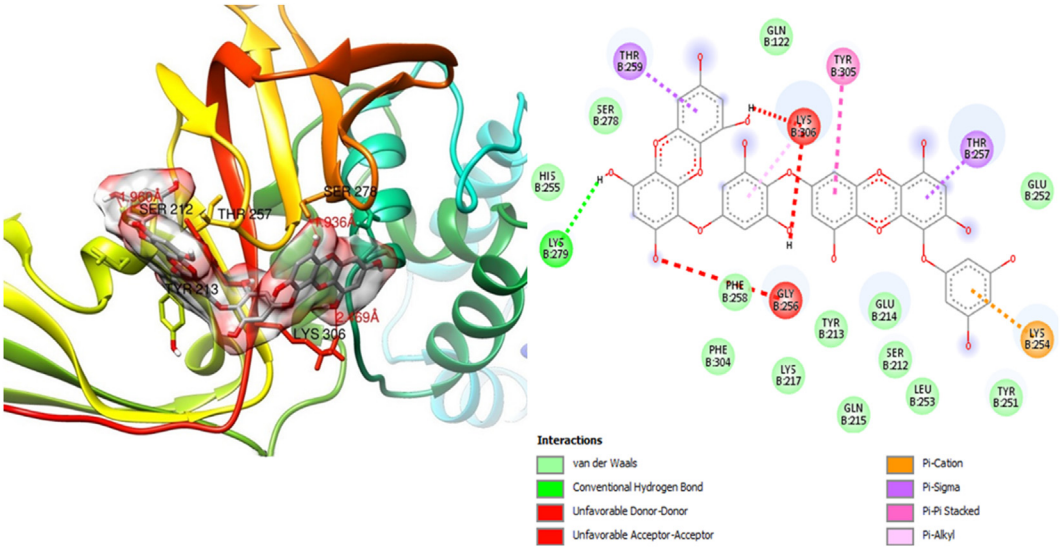

FIGURE 25.5 Molecular interactions of Dieckol with Papain-like protease of SARS-CoV-2. Three-dimensional left—ligand in the binding site of the target proteins; Two-dimensional right—ligand interactions with the amino acid residues of the SARS-CoV-2 target proteins binding site.

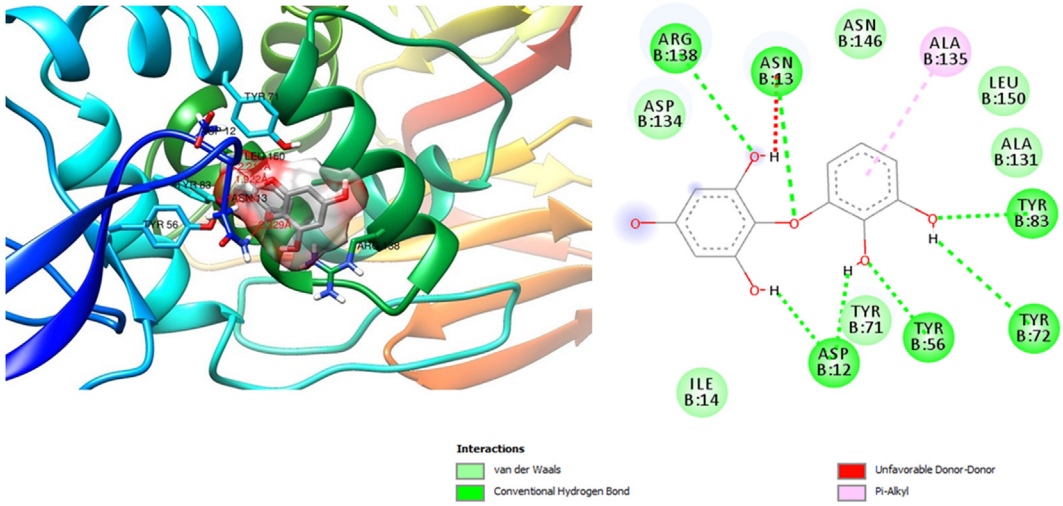

FIGURE 25.6 Molecular interactions of ZINC82312352—dieckol derivative with Papain-like protease of SARS-CoV-2. Three-dimensional left—ligand in the binding site of the target proteins; Two-dimensional right—ligand interactions with the amino acid residues of the SARS-CoV-2 target proteins binding site.

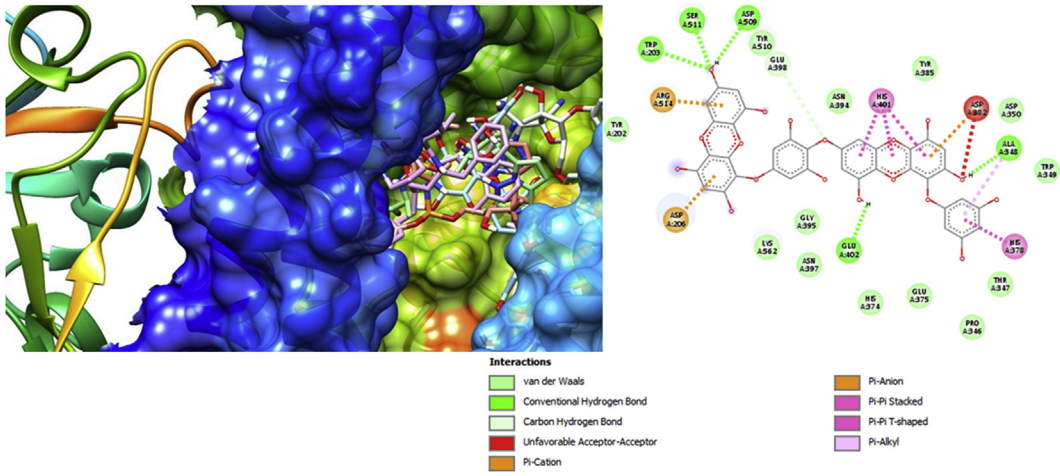

FIGURE 25.7 (A) Dieckol, Lopinavir, CHEMBL3120784, GS-6620, SCHEMBL10142598 and WD5DUG7X38 at the binding pocket of ACE2 complex with Spike protein. (B) Interactions of Dieckol with ACE2 complex with spike protein of SARS-CoV-2.

4. Discussion

The molecular docking analysis of the five antiviral agents and their derivatives show that dieckol has the highest binding affinity with all the SARS-CoV-2 target proteins—spike (S) protein, RdRp, 3CLpro, PLpro, and main protease (Table 25.1). Dieckol is a phlorotannin made up of two monomeric structures of eckol, a polyphenolic compound.

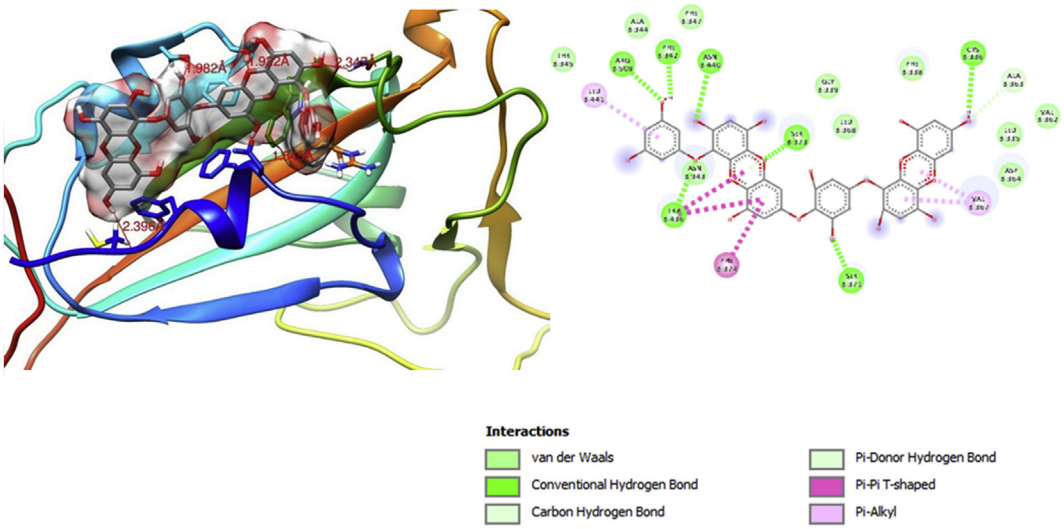

FIGURE 25.8 Molecular interactions of Dieckol with Spike protein of SARS-CoV-23D left—ligand in the binding site of the target proteins; Two-dimensional right—ligand interactions with the amino acid residues of the SARS-CoV-2 target proteins binding site.

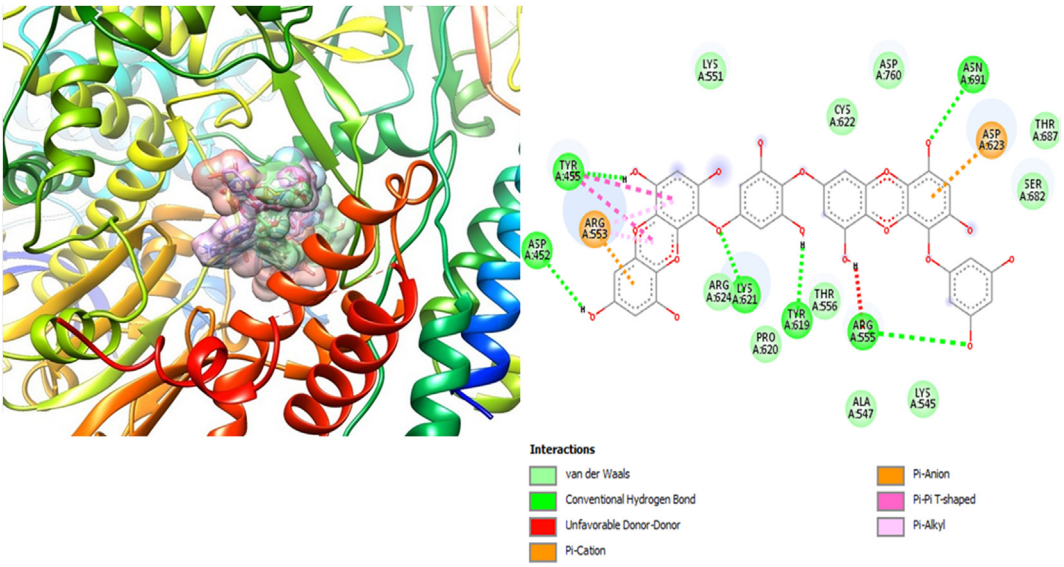

FIGURE 25.9 Right = Molecular interactions of Dieckol, Remdesivir, Ritonavir, WD5DUG7X38 at the same binding site of RdRp of SARS-CoV-2. Left = Two-dimensional interactions of Dieckol with RdRp of SARS-CoV-2.

It has been reported that dieckol has antiviral, antitumor, antidiabetic, antioxidant, antiinflammatory, antiadipogenic, and radio-protective effects [9,20–23]. Dieckol has shown broad-spectrum antiviral activity against viruses such as porcine epidemic diarrhea virus, viral hemorrhagic septicemia virus, human papillomavirus, murine norovirus, human immunodeficiency virus, and coronavirus (SAR-CoV) [9,23,24]. Park et al. 2013 showed that dieckol isolated from the edible brown algae *Ecklonia cava* is a SARS-CoV 3CLpro inhibitor. In this study, we found that dieckol was able to dock in the binding site of SARS-CoV-2 target proteins with additional hydrogen among others. This may explain why dieckol had the highest binding affinity than the other chemical compounds that were screened. It is, therefore, possible that dieckol could inhibit SARS-CoV-2 activity by blocking the active site of its target proteins in the groove.

Lipophilicity is a major factor that contributes to the ADMET characteristics of drugs and a limit of log $P < 5$ according to Lipinski is, therefore, an acceptable lipophilicity range for compounds reaching Phase II clinical trials [25,26]. Dieckol, from the result obtained from five different lipophilicity model of SwissADME (Table 25.4), showed positive. These positive values signify that the molecules have an optimal lipophilic property and fulfill the essential criteria for drug molecules, Log $P < 5$ [19]. Also, the water solubility predictions from SwissADME (Table 25.3) showed dieckol to be moderately water-soluble. This suggests that the molecules may be administered in the body through an oral or parenteral route. Furthermore, the toxicity test from PROTOX-II showed that dieckol is relatively not toxic to the human host's toxicity targets and toxicological pathways (Table 25.5).

Lopinavir in combination with Ritonavir is another therapy with good inhibitory activity against the 2019-nCoV. Ritonavir was reported to inhibit the metabolizing enzyme cytochrome P450 3A and therefore increases the half-life of Lopinavir [16,26–28]. In this study, Lopinavir showed relatively high-binding affinity and effectively docked with the binding site of 3CL-pro and RdRp target proteins of SARS-CoV-2. This may explain the potential inhibitory activity of lopinavir against SARS-CoV-2 (Table 25.1 and Fig. 25.5). The molecule relatively fulfills the Lipinski rule of 5, have moderate water solubility, GI absorption, bioavailability, synthetic accessibility, and optimal lipophilicity as expressed on Tables 25.3 and 25.4, respectively. PROTOX-II test showed that lopinavir is relatively not toxic to the host's toxicity targets and toxicological pathways (Table 25.5).

Although Chloroquine has been reported to have inhibitory activity against 2019-nCoV, its binding affinity with all the target proteins in this study was relatively low (Table 25.1 and Fig. 25.1). This observation suggests that its mechanism of action may not necessarily be through direct inhibition of the viral proteins. Smith et al., suggested that acidification of the cell membrane surface receptor and immunomodulation of cytokine release may be the mechanism used by chloroquine to inhibit fusion of the viral spike protein with ACE2 of the human host [28].

5. Conclusion

The results obtained in this study suggest that dieckol, lopinavir, and ritonavir possessed inhibitory potential against SARS-CoV-2 targets spike (S) protein, 3CLpro, RdRp, and PLpro. They were also found to possess acceptable ADMET properties. These compounds could therefore be further explored in the establishment of therapeutic interventions against COVID-19.

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