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Investigation of Potential Activity of Some Organic Compounds and Antiviral Drugs Against COVID-19 Based on Molecular Docking

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Abstract

The current outbreak of the COVID-19 threatens public health worldwide, and WHO declares this as a global pandemic. Effective oral drug therapy against coronavirus did not discover yet. In order to find out an effective drug, we docked 23 compounds within the active site of 6LU7 protein of coronavirus. Among all, some antivirals exhibited very promising results against coronavirus and may be considered as a potential drug for treating COVID-19 disease. Molecular docking study revealed that isovitexin and apigenin found from nishinda (*Vitex sp.*) as well as our newly prepared compound (E)-4-((3,5-dibromo-2-hydroxybenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide showed excellent activity as compared to danoprevir, lopinavir, remdesivir and ritonavir. Isovitexin showed a binding affinity of -8.00 kcal/mol, whereas the binding affinity of sulfonamide compound with the coronavirus protein was -7.30 kcal/mol, which was relatively high compared to other antiviral drugs. Besides, the synthesized sulfonamide compound's absorption, distribution, metabolism, excretion, and toxicity profiles were also carried out. The compound showed excellent drug-like properties and percentage of human oral absorption. Moreover, it was found to be safe for the human body in toxicological risk assessment.

Keywords: COVID-19; Molecular docking; Isovitexin; Sulfonamide compound; ADMET.

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1. Introduction

In December 2019, an outbreak occurred with the flu-like syndrome and pneumonia in Wuhan City, Hubei Province of China [1,2]. It is thought to spread from a local seafood market [3]. Soon the virus was isolated from the human and molecular analysis showed that the pathogen was a novel coronavirus, first named 2019-nCoV, and WHO renamed this disease as COVID-19 [4], which is genetically closely related to previous outbreaks of SARS (2002-2004) and MERS (2012). Compared to SARS and MERS, COVID-19 is less lethal but highly contagious [5]. The International Committee on Taxonomy of Viruses (ICTV) proposed the name of the virus as SARS-CoV-2 [6,7]. It causes severe respiratory infection, and the common symptoms include dry cough, fever, tachypnea,

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fatigue, sore throat, muscle pain, headache, sneezing, and diarrhea [8]. This virus is rapidly spread to other provinces of China and most of the world's countries due to its efficient person-to-person transmission and high contagious nature [9]. On January 30, 2020, WHO declared this outbreak a public health emergency of international concern (PHEIC). Due to the explosive increase of affected people WHO characterized COVID-19 as a pandemic on March 11, 2020. Immune compromised people with preexisting health vulnerabilities are at greater risk. According to Worldometer, till October 5, 2021, more than 200 countries and territories are affected, with 236,364,710 confirmed cases and 4,826,202 deaths. The exact transmission and etiology of coronavirus are still unclear. Scientists have recently discovered some vaccines, but how long the vaccines will protect an individual is unclear.

At present, there are no specific drugs available to fight COVID-19. Scientists around the world from different research institutions are working relentlessly to discover effective therapies against COVID-19. As several antiviral drugs such as remdesivir, lopinavir, ritonavir were effective in MERS CoV [10], several trials were done to assess the efficacy of remdesivir against moderate or severe COVID-19 [11,12]. A few combination therapies with protease inhibitor lopinavir-ritonavir have also been reported to treat COVID-19, which is currently used to treat HIV. Other drugs of interest include chloroquine [13], hydroxychloroquine, tocilizumab, which were also used to evaluate their efficacy against coronaviruses [14-17]. Moreover, several drugs such as immune enhancers or antiviral drugs, including ribavirin, arbidol, favipiravir, have also been recommended as potential investigational drugs [18]. Food and Drug Administration (FDA) approved emergency use of chloroquine and hydroxychloroquine at the end of March 2020 to treat COVID-19 [19]. In addition, an antiviral drug, favipiravir, also reported treating COVID-19 which has also been undergone clinical trial [20]. Some studies reported that dexamethasone and enoxaparin were also used to decrease the death rate in severely ill COVID-19 patients. Another in-vivo research has revealed that ivermectin can significantly attenuate the level of SARS-CoV-2 viral RNA [21].

In this present study, we focus on finding out the possible therapeutic candidates that will be considered effective drug therapy against COVID-19. To search for a potential candidate, we synthesized a new organic sulfonamide compound and performed molecular docking with coronavirus protease to monitor how they interact. Molecular docking is an essential computational tool in drug discovery programs, which was used for the small ligand as a guest with various protein receptors as host. This docking-based methodology is highly used to predict the affinity of a compound and target protein. Molecular docking investigation can be carried out using known ligands (such as naturally occurring molecules or known drugs) or novel ligands. In this paper, we also performed molecular docking of some promising antiviral drugs and several medicinal compounds found in Tulasi (*Ocimum sp.)*, Kalonji (*Nigella sp.*), and Nishinda (*Vitex sp.*) to explore their activity against COVID-19. In addition, we performed ADMET predictions of our newly synthesized compound to evaluate its physicochemical and pharmacological profiles and assess its drug-likeness as well as toxicity risk assessment. The stage of drug

development is a long, tiring, and tedious process. ADMET prediction can significantly reduce this time resources and money [22,23]. A study showed that a safety assessment could reduce about halves of the adverse drug reactions of a drug [24]. So, accurate prediction of ADMET can sort out unresponsive or unsafe leads before going to wet lab analysis. The study results suggested that medicinal components of Tulasi, Kalonji, Nishinda, and our synthesized compound and some antiviral drugs showed promising effects against coronavirus and needed further in-vivo assessment to explore more information.

2. Materials and Methods

2.1. *Preparation of sulfonamide compound*

A new crystal Schiff-based (E)-4-((3,5-dibromo-2-hydroxybenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (sulfonamide compound) has been derived from the condensation of sulfamethoxazole and 3,5-dibromosalicylaldehyde. This compound was experimentally characterized by melting point, FT-IR, and UV-VIS spectroscopic data. The molecular structure of the compound has also been studied using single-crystal X-ray structure techniques. The crystal structure of the compound is shown in Fig. 1.

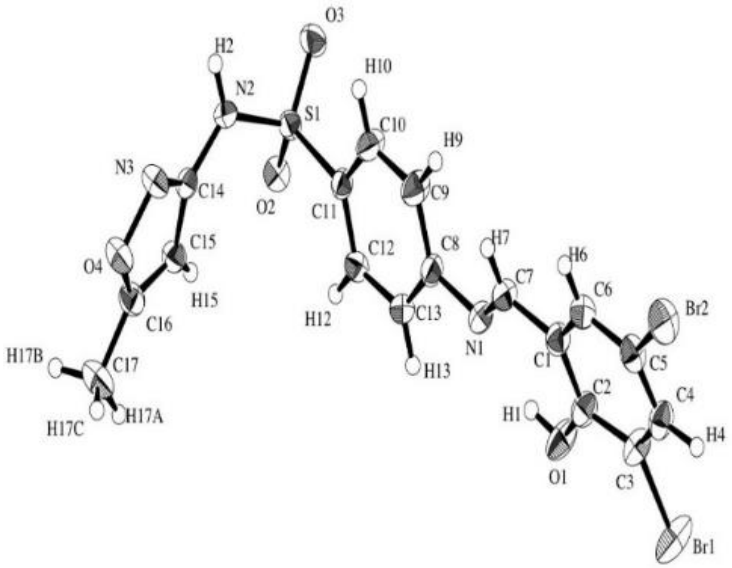

Fig. 1. Structure of sulfonamide compound.

2.2. *Computational methodology*

The structure of the compound (single crystal structure) was drawn using GaussView 6.0.16 software, and other compounds were collected from PubChem as a pdf file. The

density functional theory (DFT) was applied for complete molecular geometry optimization of the crystal compound at the B3LYP level and 6-31G+(d, p) basis set with the help of software package Gaussian 09W. The molecular docking simulation of the optimized crystal structure was investigated using PyMol and PyRx software. The coronavirus's target protein (PDB code: 6LU7) was downloaded as pdb format from the pdb server. The optimization of all species with energy minimization was performed by PyMol. The energy minimized sulfonamide compound, drug components, and collected protein was then used as input in PyRx and PyMol software for molecular docking simulations. Discovery studio 4.5 software was used to evaluate the docking mode of the ligand-protein complex. In this study, ADME properties were calculated using the Qikprop v3.10 tool of Schrödinger. Besides, toxicity profiles of the compound were assessed by ProTox II. In addition, the inhibition constant of studied compounds was done using the equation $K_i = \exp(\Delta G/RT)$ at room temperature.

3. Results and Discussion

3.1. *Molecular docking*

The binding affinities or docking scores of investigated compounds are tabulated in Table 1 with their constant inhibition value. The obtained docking results of various medicinal and drug components with the target protein, 6LU7 of a novel coronavirus, reveal that the drug component, danoprevir interacted with ARG131, THR135, LYS137, ASP197, and ASN133 via hydrogen bond. Besides, it was also mutually attached with LEU286 and LEU287 amino acids residues through two hydrophobic interactions (Fig. 2).

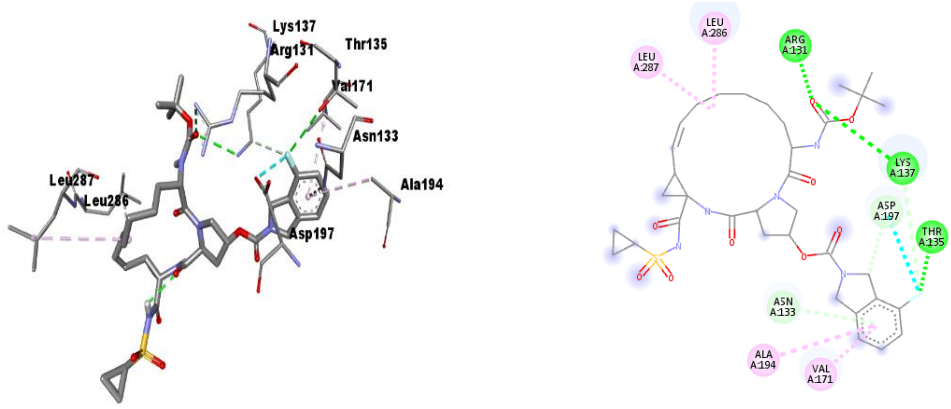

Fig. 2. Docking mode of danoprevir with 6LU7.

Table 1. Binding affinity and inhibition constant of all compounds.

Sl	Component	Binding affinity (kcal/mol)	Inhibition constant
1	Danoprevir	-8.40	0.695
2	Isovitexin	-8.00	1.366
3	Lopinavir	-7.80	1.914
4	Apigenin	-7.80	1.914
5	Remdesivir	-7.50	3.176
6	Ritonavir	-7.40	3.760
7	Sulfonamide compound	-7.30	4.452
8	Galidesivir	-7.20	5.270
9	Efavirenz	-7.20	5.270
10	Baricitinib	-6.80	10.353
11	Zidovudine	-6.40	20.337
12	Ribavirin	-6.10	33.745
13	Beta-caryophyllene	-6.00	39.950
14	Emtricitabine	-5.90	47.296
15	Beta-elemene	-5.80	55.993
16	Lamivudine	-5.70	66.289
17	Tenofovir	-5.70	66.289
18	Thymohydroquinone	-5.30	130.219
19	Favipiravir	-5.10	182.511
20	Chloroquine	-5.00	216.072
21	Thymoquinone	-5.00	216.072
22	Methyl eugenol	-4.90	255.803
23	Para-cymene	-4.90	255.803

Based on the docking analysis, the medicinal component of nishinda (*Vitex sp.*), isovitexin were closely linked with the amino acids LEU141, SER144, and CYS145 by the hydrogen bond. In addition, two hydrophobic interactions with THR190, ALA191, and PRO168 were seen in the docking pocket (Fig. 3).

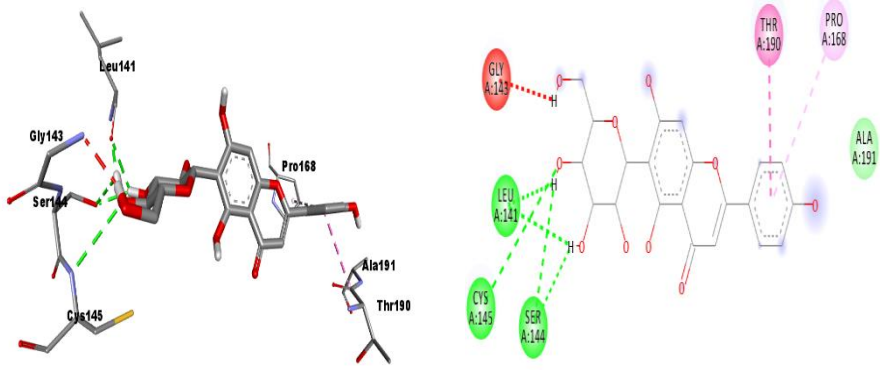

Fig. 3. Docking mode of isovitexin with 6LU7.

The docking pose of lopinavir expressed that various amino acid residues of the target protein mentioned above were tightly bound with lopinavir via only hydrophobic

interactions (Fig. 4). The binding pose of apigenin was combined with residues TYR54, LEU141, SER144, and GLU166 through hydrogen bonding. One hydrophobic interaction was found between apigenin and MET49 amino acid (Fig. 5).

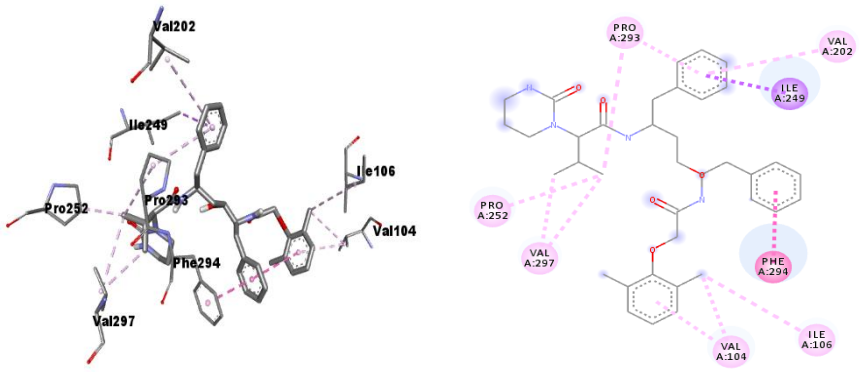

Fig. 4. Docking mode of lopinavir with 6LU7.

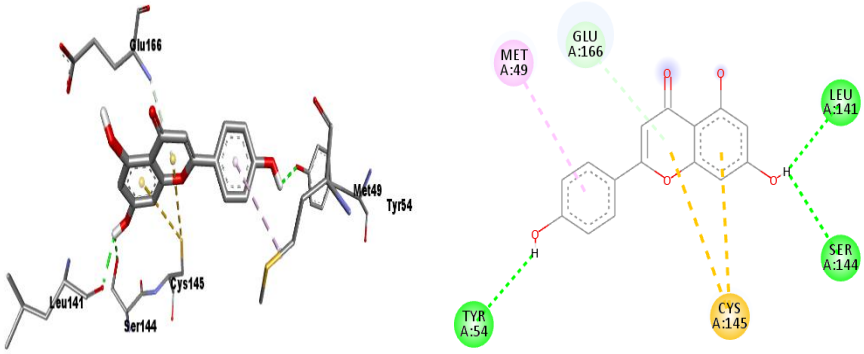

Fig. 5. Docking mode of apigenin with 6LU7.

Remdesivir has displayed hydrogen bond interactions with ASN142, HIS163, SER144, and HIS163 and hydrophobic interaction with MET49 of the target protein, 6LU7 (Fig. 6). The active docking site of ritonavir indicated that the amino acid residues GLN189, ASN119, and GLU166 were added with ritonavir through hydrogen bond interactions. While HIS41, MET165, LEU27, and CYS145 residues were strongly linked with ritonavir via hydrophobic interactions (Fig. 7).

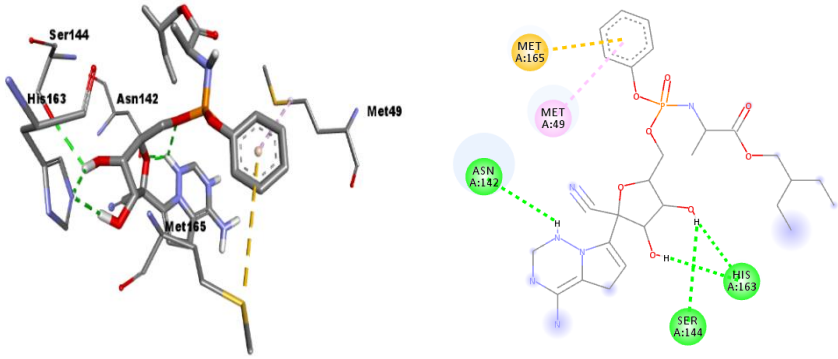

Fig. 6. Docking mode of remdesivir with 6LU7.

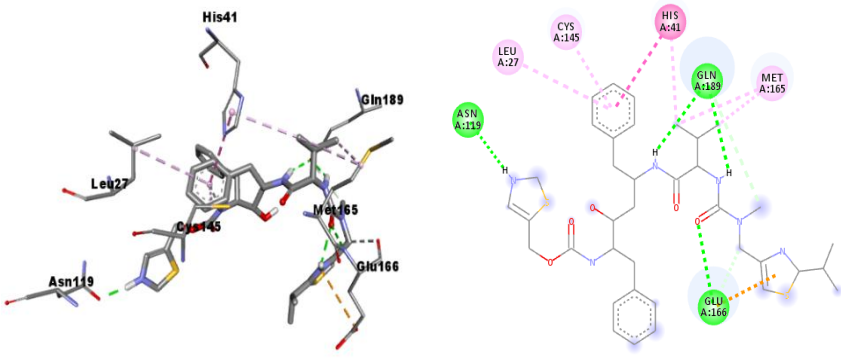

Fig. 7. Docking mode of ritonavir with 6LU7.

The synthesized sulfonamide compound exhibited significant binding energy -7.30 kcal/mol compared to some antiviral drugs (Table 1). Besides, in the docking pose, this component was bound with THR26, GLY143, and CYS145 residues through hydrogen bonding interactions. Besides, many hydrophobic interactions were shown with THR25, GLN189, THR190, MET165, LEU167, and PRO168 amino acid residues of enzyme of novel coronavirus (Fig. 8).

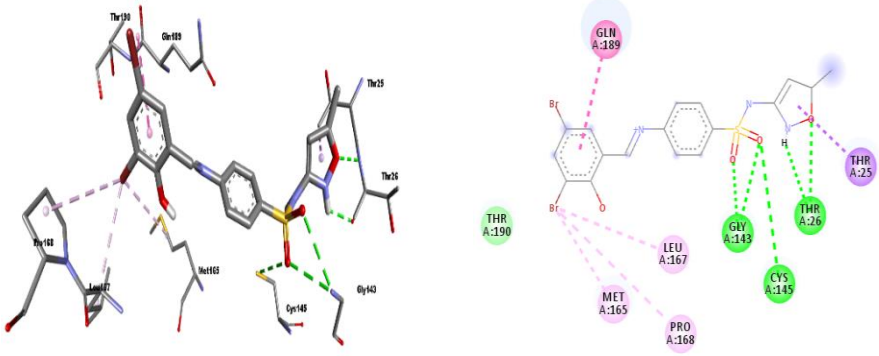

Fig. 8. Docking mode of sulfonamide compound with 6LU7.

Galidesivir drug was linked with target protein by only hydrogen bond interactions to GLU166, SER144, PHE140, and GLY143. Efavirenz was formed hydrogen bonds with THR111 and ASN151 amino acid residues in its binding site. Moreover, hydrophobic interactions were seen between efavirenz and PHE294 residue. In the case of baricitinib binding site, HIS41, THR24, GLY143, CTS145, GLN189, HIS41, HIS164, and THR25 amino acids were bound with it through all hydrogen bonds. The compound zidovudine was tightly combined to the target protein via hydrogen bonds with SER144, GLN189, GLU166, GLY143, SER144, CYS145, ASN142 residues, while it hydrophobically also interacted to CYS145 residue. The docking result of ribavirin informed that the amino acids residues ASN142, LEU141, HIS164, SER144, and CYS145 were bound with it via hydrogen bond interactions. The beta-caryophyllene of *Ocimum sp.* was hydrophobically interacted with Val104, PHE8, and PHE294 amino acid residues. SER144, HIS163, PHE140, GLU166, CYS145, and ASN142 residues of target protein were linked with emtricitabine drugs through hydrogen bond interactions. On the other hand, CYS145 amino acid was also linked with drugs via hydrophobic interaction. The medicinal compound beta-elemene was attached with merely hydrophobic interactions with PHE294, VAL104, ILE106, PHE8, and PHE294 amino acid residues.

The lamivudine drug was combined with LEU141, SER144, HIS163, HIS164, PHE140, GLU166, SER144, and CYS145 of amino acid residues the target protein through hydrogen bonding. One hydrophobic interaction was seen between lamivudine and CYS145 residue. The active docking site of tenofovir indicated that it was bound with the amino acid residues THR111, ASP295, ARG105, GLN110, and THR292 via hydrogen bonding interactions. At the same time, PHE294 residue was attached with tenofovir via hydrophobic interaction. The docking studies at the active site of 6LU7 showed that its LEU220 amino acid residue interacted with the thymohydroquinone component of *Nigella sp.* through a hydrogen bond. Besides, LEU271, TRP218, and PHE223 residues were hydrophobically attached with thymohydroquinone.

The docking case of favipiravir with 6LU7 protein revealed that it was shown to have hydrogen bonding with ASN142, SER144, GLU166, PHE140, and GLY143 residues. SER158 amino acid of the target protein interacted with chloroquine drug via hydrogen bond. While PHE294 and VAL104 residues were hydrophobically linked with chloroquine in the active site. The thymoquinone component of *Nigella sp.* was attached with the target protein's amino acids LYS5, TRP207, and SER284 through hydrogen bonding. Besides, it was bound with the target's PHE291, LEU282, PHE3, TRP207, and PHE291 residues via hydrophobic interactions. In this study, hydrogen bonding was formed between the methyl eugenol component of *Ocimum sp.* and CYS145 residue. Hydrophobic interactions were seen between methyl eugenol and HIS41, MET49, and MET165 amino acids of the target. The medicinal component of para-cymene of *Nigella sp.* was bound with the LEU271, TRP218, and PHE223 residues via hydrophobic interactions.

3.2. *ADMET investigation*

3.2.1. *Assessment of drug-likeness*

In the ADMET investigation, the Drug-likeness of the compound was evaluated by RO5 (Lipinski's rule of five) and Jorgensen's rule of three. RO5 is generally considered as a thumb rule for distinguishing drug-like and unlike compounds. Our newly synthesized compound follows all parameters other than one violation (molecular weight). Moreover, the compound is also fit for the rule of three (Table 2).

Table 2. Assessment of drug-likeness for sulfonamide compound.

Compound	Rule of five				Rule of three		
Sulfonamide	Hydrogen bond donors	Hydrogen bond acceptors	Molecular mass	Octanol-water partition coefficient	QPlogS	QPPCaco	Primary Metabolites
	2	7	515.17	3.20	-5.7	257.76	2

3.2.2. *Prediction of lipophilicity, solubility and oral absorption*

Lipophilicity is directly related to drug solubility, permeability, and absorption. To be absorbed, a drug must have good aqueous solubility and the capability to permeate across biological membranes [25–27]. The observed value of lipophilicity, QPlogPo/w, and solubility, QPlogS are 3.2 and -5.7, respectively (Table 3). The compound also showed promising human oral absorption.

Table 3. Prediction of ADME properties for sulfonamide compound.

Parameters	Predicted value	Parameters	Predicted value	Parameters	Predicted value
HBD	2	QPlogS	-5.7	QPPCaco	257.75
HBA	7	QPlogPw	13.51	QPPMDCK	769.01
Molecular weight	515.17	QPlogPo/w	3.2	Human Oral Absorption	3
PSA	104.74	QPlogKhsa	0.045	% Human Oral Absorption	75.90
metab	2	QPlogBB	-1.32	CNS	-2
#rotor	7	QPlogKp	-2.94	QPloghERG	-6.44

3.2.3. *Blood–brain barrier and dermal penetration*

Drugs may produce toxicity if they penetrate through the blood-brain barrier. So, it is preferable not to enter the brain other than CNS active drugs. The CNS activity is predicted on a scale of CNS inactive -2 to CNS active +2. From Table 3, it is found that the compound is CNS inactive. Besides, some drugs are needed to administer via the

dermal route. QPlogKp is used to predict skin permeability. The QPlogKp value of the sulfonamide compound lay in the recommended range (Table 3).

3.2.4. *prediction of plasma-protein binding and metabolism*

Drugs with a high affinity for plasma proteins may show less bioavailability and cause various drug-drug interactions [28]. QPlogKhsa can predict plasma protein binding. The value of QPlogKhsa for the sulfonamide compound was found within the recommended range (Table 3).

3.2.5. *Toxicity risk assessment*

Many drug candidates fail to reach the market due to toxicity issues. The toxic dose is calculated by its LD_{50} dose (mg/kg body weight). LD_{50} for the compound is 3471 mg/kg, which is relatively safer and belongs to class 5 in the toxicity class [Class I: fatal, $LD_{50} \leq 5$; Class II: fatal, $5 < LD_{50} \leq 50$; Class III: toxic, $50 < LD_{50} \leq 300$; Class IV: harmful, $300 < LD_{50} \leq 2000$; Class V: may be harmful, $2000 < LD_{50} \leq 5000$; Class VI: non-toxic, $LD_{50} > 5000$]. Moreover, the compound has no carcinogenicity, immunotoxicity, mutagenicity, or cytotoxicity (Table 4).

Table 4. Oral toxicity prediction results (Using ProTox II).

Target	Prediction	Target	Prediction
LD_{50}	3471 mg/kg	Immunotoxicity	Inactive (Probability 0.98)
Hepatotoxicity	Active (Probability 0.64)	Mutagenicity	Inactive (Probability 0.80)
Carcinogenicity	Inactive (Probability 0.50)	Cytotoxicity	Inactive (Probability 0.76)

The hERG toxicity is one of the major concerns in drug development. It is associated with QT interval prolongation and potentially produces cardiotoxicity. From the predicted value, the compound showed no hERG toxicity (Table 3).

4. Conclusion

Molecular docking of the sulfonamide compound, various medicinal compounds, and antiviral drugs were investigated against the target protein of 6LU7 of novel coronavirus. Several components were shown to inhibit the enzyme of novel coronavirus strongly. The results of docking studies revealed that various docked components have higher binding energy values. Among the 23 components, the first eight showed better activity against 6LU7 of novel coronavirus with higher binding value within -7.30 to -8.40 kcal/mol and can be considered potential candidates against COVID-19. Among all the components, isovitexin and apigenin (found from *Vitex sp.*) were comparatively potent against 6LU7 compared to danoprevir and lopinavir drug components. While the sulfonamide compound was exhibited significant value as compared to remdesivir and ritonavir.

Moreover, the synthesized sulfonamide compound has nearly the same binding affinity as galidesivir and efavirenz. Besides, this sulfonamide compound has higher binding energy than baricitinib, zidovudine, and ribavirin drugs. At the same time, beta-caryophyllene and beta-elemene components of *Ocimum sp.* exhibited equivalent binding energy concerning ribavirin and emtricitabine drugs. In addition, the rest of the components were shown to have lower binding activity than other components against the enzyme of coronavirus, 6LU7.

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