Indonesian Journal of Chemical Research

http://ojs3.unpatti.ac.id/index.php/ijcr Indo. J. Chem. Res., 9(3), 150-162, 2022

Molecular Docking Study of Chalcone Derivatives as Potential Inhibitors of SARS-CoV-2 Main Protease

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Received: September 2021
Received in revised: September 2021
Accepted: January 2022
Available online: January 2022

Abstract

SARS-CoV-2 main protease is a potential target for the development of AntiCOVID-19. Several chalcones have inhibitory activity against 3CL^{pro} SARS-CoV and 3CL^{pro} MERS-CoV. This study aims to predict the potential of chalcones in inhibiting 3CL^{pro} SARS-CoV-2, which plays a role in the viral replication process. In silico research carried the prediction through molecular docking toward proteins with PDB ID 6LU7 and 6Y2F. Compound K27 has a docking score more negative than lopinavir. This result indicates that compound K27 is predicted to inhibit the SARS-CoV-2 replication.

Keywords: COVID-19, SARS-CoV-2, SARS-CoV, MERS-CoV, 3CL^{pro}, chalcone

INTRODUCTION

SARS-CoV-2 is a virus from the Coronavirus group that spreads very quickly throughout the world and causes COVID-19 disease in millions of people worldwide. SARS-CoV-2 infects host cells by involving several proteins from the virus and proteins from the host. Main protease SARS-CoV-2 or chymotrypsin-like protease (3CL^{pro}) is a protein that plays a role in the viral replication process and is very important for the life cycle of life SARS-CoV-2 (Khan, Zia, Ashraf, Uddin, & Ul-Haq, 2020). Therefore, 3CL^{pro} main protease is one of the potential targets in treating COVID-19.

Until now, a drug has not been explicitly found used to treat COVID-19. Treatment therapy for COVID-19 patients is administering drugs that have been circulating. These drugs are antiviral drugs such as oseltamivir, ritonavir, lopinavir, and remdesivier. The other treatment is using antimalarial drugs such as chloroquine phosphate. Also, therapy with herbal plants (Alam, 2020; Instiaty et al., 2020).

Chalcone 1,3-diphenylprop-2-en-1-one) is a natural compound widely contained in plants and is a precursor of flavonoids and isoflavonoids. Chalcone can also be synthesized through condensation reactions, namely the Claisen Schmidt condensation and Aldol condensation (Chavan et al., 2016). Chalcone-derived compounds can be antivirals against the Coronavirus class through the primary protease inhibitory mechanism. (Park et al., 2016a) showed that chalcone-derived compounds isolated from the *Angelica keiskei* plant could inhibit the protease enzyme (3CL^{pro}) SARS-CoV activity. Broussochalcone A and B isolated from the roots of *Broussonetia papyrifera* were shown to inhibit 3CL^{pro} SARS-CoV and 3CL^{pro} MERS-CoV (Park et al., 2017). Other derivatives of chalcone compounds, namely helichrysetin and isobavachalcone, are also known to inhibit the enzymatic activity of 3CL^{pro} (MERS-CoV) (Jo, Kim, Kim, Shin, & Kim, 2019). (Ullrich & Nitsche, 2020) stated that there were similarities in the crystal structure and active sites of the main proteases SARS-CoV-2 (GDP: 6Y2E), SARS-CoV (GDP: 2BX4), and MERS-CoV (GDP: 5C3N). Therefore, chalcone compounds and their derivatives may also have inhibitory activity against 3CL^{pro} SARS-CoV-2.

Several in silico studies through molecular docking of chalcone-derived compounds have been carried out, such as the indole-chalcone-derived compound that was docked against the main protease SARS-CoV-2 (GDP: 6YB7) (Vijayakumar, Ramesh, Joji, Jayachandra, & Kannan, 2020) and (E)-1-(2,4-dichlorophenyl)-3-[4-(morpholin-4-yl)phenyl]prop-2-en-1-one with *main protease* SARS-CoV-2 (GDP: 7BQY) (Alsafi, Hughes, & Said, 2020). The research from (Alaaeldin, Mustafa, Abuo-Rahma, & Fathy, 2021) showed that the results of docking compound -(4-(N-substituted-carbamoyl-methyl)piperazine-1yl)-chalcone were in line with the results of in vitro studies of the main protease SARS-CoV-2, which exerted a significant inhibitory effect.

In this study, molecular docking of chalcone-derived compounds both derived from natural and

synthetic materials was carried out to predict their interaction with the active site of $3CL^{pro}$ SARS-CoV-2 (GDP: 6LU7 and 6Y2F). The interaction between the ligand-receptors was analyzed based on the scores or docking scores obtained. This docking score can predict the stability of the ligand-receptor complex. Molecular docking can also predict the type of interaction formed between ligands and amino acid residues on the protein's active site (Gaspersz & Sohilait, 2019; Mulyati & Panjaitan, 2021).

METHODOLOGY

Hardware

The hardware in this research uses Asus ROG STRIX with specification Intel Core-i7-9750H CPU @2.60GHz processor, 1 TB RAM, GPU GTX 1050.

Software

The software used in this research is YASARA (*Yet Another Scientific Artificial Reality Application*), Marvin Sketch, PLANTS (*Protein-Ligand ANT System*), and Discovery Studio Visualizer.

Receptor Preparation

The $3CL^{pro}$ SARS-CoV-2 receptor used is a protein with PDB codes 6LU7 and 6Y2F obtained based on a literature search (Jin et al., 2020; Zhang et al., 2020) and downloaded from the Protein Data Bank (GDP) database (http://www.rscb.org.pdb). The two proteins' 3-dimensional (3D) structure was prepared using YASARA by removing water molecules and hydrogen atoms. In the YASARA, the separation between proteins and native ligands is also carried out. The separated protein and native ligand structure are then stored in the file.mol2.

Ligand Preparation

Native ligands were obtained from proteins with PDB codes 6LU7 and 6Y2F downloaded from the PDB database. The native ligands were separated from the protein using the YASARA program. Chalcone derivative compounds were obtained based on kinds of literature search (Cole, Hossain, Cole, & Phanstiel, 2016; Jo et al., 2019; Kim, Ryu, Shim, Park, & Withers, 2009; Mahapatra, Bharti, & Asati, 2015; Park et al., 2016b, 2017; Sashidhara et al., 2012; Smit & N'Da, 2014; Troeberg et al., 2000; Wang, Ding, Liu, & Zheng, 2004; Xu, Wan, Dong, But, & Foo, 2000; Yadav et al., 2012). The two-dimensional structure of the chalcone and lopinavir derivatives was downloaded from the PubChem database (http://PubChem.ncbi. nlm.nih.gov) in the form of an SDF file. All ligands, whether native ligands, chalcone-derived compounds, or lopinavir, which compare drug compounds, were then prepared using the Marvin Sketch program. In this process, the ligands were conditioned at pH 7.4, and a conformational search was carried out. The conformational structure of the ligands is saved in the form of file.mol2.

Validation Method

The molecular docking method (redocking) was validated by docking the native ligand with its receptor using the PLANTS program. The docking process was carried out on ten native ligand conformers. The docking results then calculate the RMSD (Root Mean Square Deviation) value using the YASARA program. The docking method is valid and acceptable if the redocking RMSD value between the active site of the receptor and the native ligand is <2.00 Å (Adelina, 2014; Bell & Zhang, 2019).

Molecular Docking

Molecular docking is done between receptors (6LU7 and 6Y2F) with ligands. The ligands are chalcone-derived compounds, and a comparison ligand (lopinavir) was carried out using the PLANTS program. The docking scores of each ligand were compared with the native ligand and the comparison ligand. The interaction between the receptor and the ligand was visualized using the Discovery Studio Visualizer.

RESULTS AND DISCUSSION

Method Validation

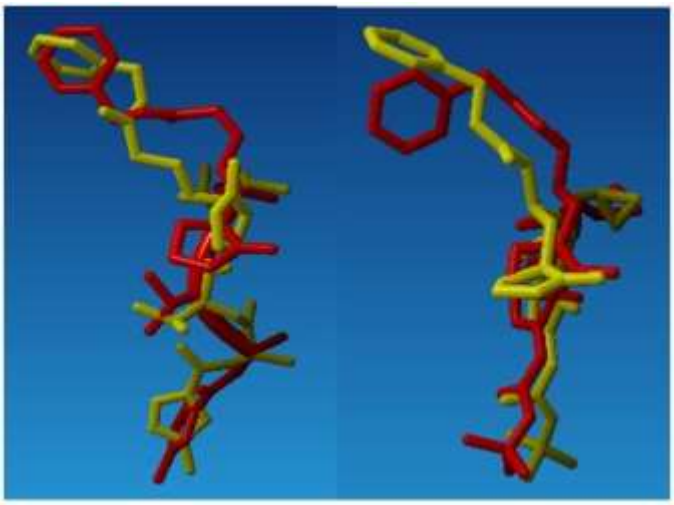
Native ligand must be redocking. Native ligand structure after redocking differs from before one (PDB) (Figure 1). The redocking results show that the protocol used in this study has been well validated. This validation is indicated by the RMSD value < 2.00 Å (Maahury & Allo, 2021). This research focuses on the redocking of 6LU7 with N3 and 6Y2F with O6K. (Table 1). RMSD value is a parameter used to evaluate the similarity of two structures based on differences in the atomic distance (Primana, 2015). The smaller the RMSD value, the more similar the conformation of the native ligand resulting from the redocking with the conformation of the native ligand from PDB (Adelina, 2014).

Molecular Docking of Chalcone Derivative Compounds

Docking of molecular docking of chalcone-derived compounds, both naturally occurring as secondary metabolites in plants and their synthesis in the laboratory (Table 2), has been tested in silico by molecular docking against the $3C^{Lpro}$ SARS-CoV-2 receptor with PDB codes 6LU7 and 6Y2F.

Table 1. RMSD *redocking* result

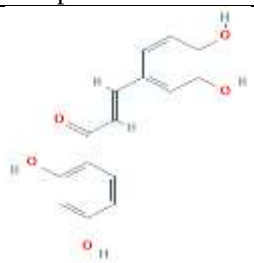
Docking Validation	RMSD (Å)
6LU7 with N3	1.7637
6Y2F with O6K	1.9443

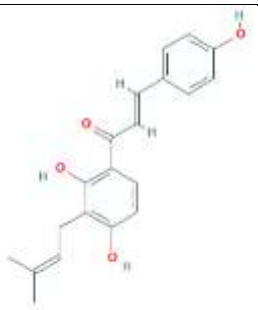
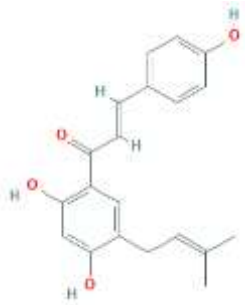
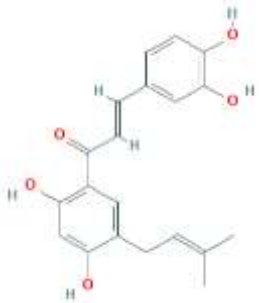
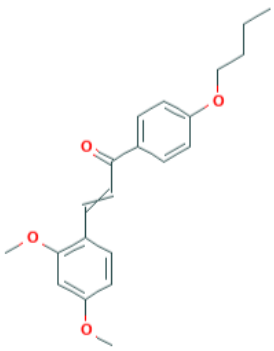


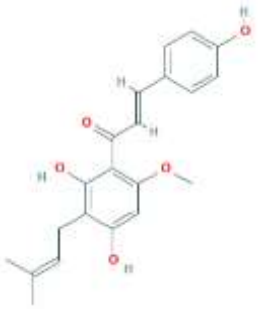
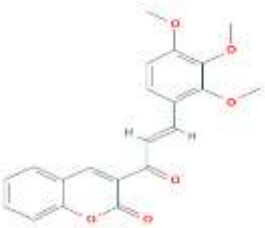
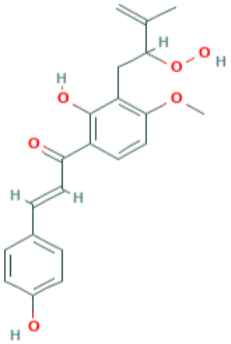
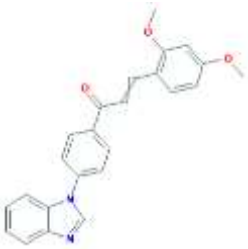
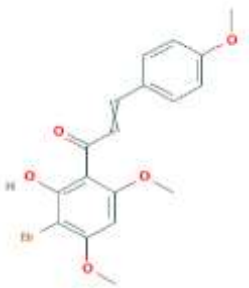
(a) (b)

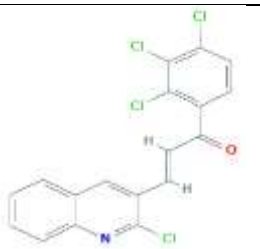
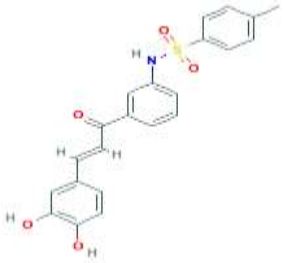
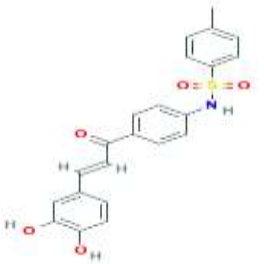
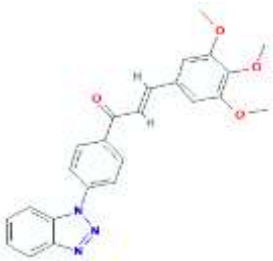
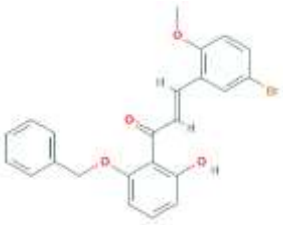
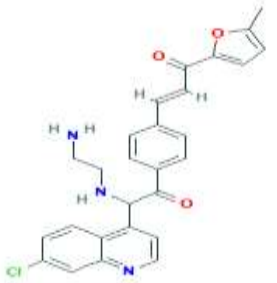
Figure 1. *Alignment native ligand* from redocking (yellow) and PDB (red). (a). N3 at 6LU7 protein (b). O6K at 6Y2F protein

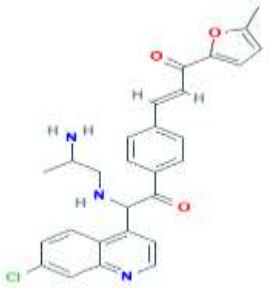
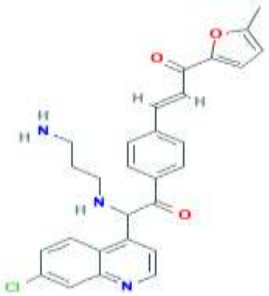
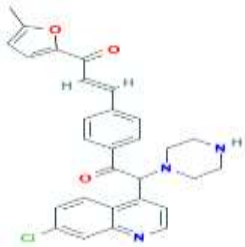
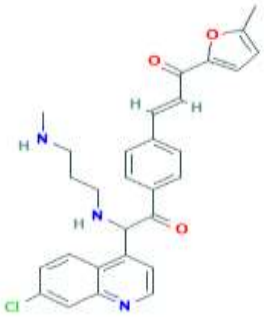
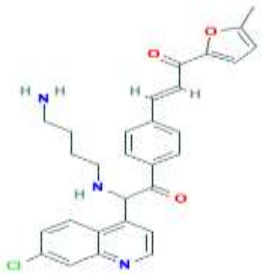
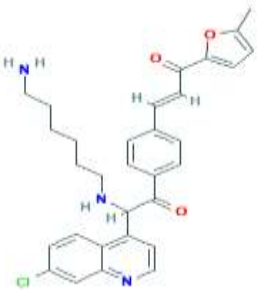
Table 2. *In silico* result of Chalcone Derivative Compounds and Comparative Ligands with $3CL^{pro}$ SARS-CoV-2 (PDB: 6LU7 and 6Y2F)

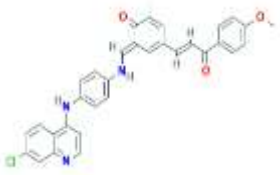
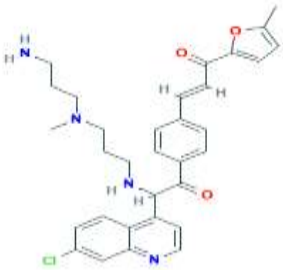
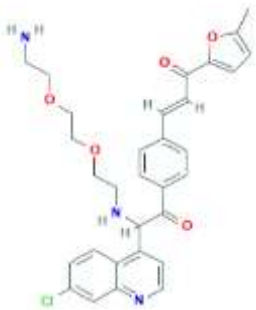
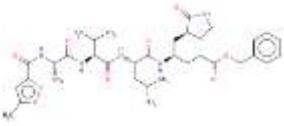
Molecule code	Chalcone Derivative Compounds name	Chalcone Derivative Compounds Structure	Docking Score 6LU7	Docking Score 6Y2F
K1	Butein ((*E*)-1-(2,4-dihydroxyphenyl)-3-(3,4-dihydroxyphenyl)prop-2-en-1-one) (CID: 5281222)		-82.550	-78.888
K2	Helichrysetin ((*E*)-1-(2,4-dihydroxy-6-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one) (CID: 6253344)		-82.924	-76.892

K3	Isobavachalcone ((*E*)-1-[2,4-dihydroxy-3-(3-methylbut-2-enyl)phenyl]-3-(4-hydroxyphenyl)prop-2-en-1-one) (CID: 5281255)		-90.540	-84.178
K4	Broussochalcone B ((*E*)-1-[2,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-3-(4-hydroxyphenyl)prop-2-en-1-one) (CID: 6450879)		-95.556	-90.710
K5	3-(2,5-dimethoxyphenyl)-1-(4-prop-2-enoxyphenyl)prop-2-en-1-one (CID: 54148406)		-81.049	-81.961
K6	Broussochalcone A ((*E*)-1-[2,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-3-(3,4-dihydroxyphenyl)prop-2-en-1-one) (CID: 6438825)		-89.664	-91.026
K7	2,4-dimethoxy-4'-butoxychalcone (1-(4-butoxyphenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one) atau 1-(4-butoxyphenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (CID: 53822675)		-83.328	-81.274

K8	Xanthohumol ((*E*)-1-[2,4-dihydroxy-6-methoxy-3-(3-methylbut-2-enyl)phenyl]-3-(4-hydroxyphenyl)prop-2-en-1-one) (CID: 639665)		-79.858	-82.131
K9	3-[(*E*)-3-(2,3,4-trimethoxyphenyl)prop-2-enoyl]chromen-2-one (CID: 46369167)		-73.184	-74.395
K10	Xanthoangelol E ((*E*)-1-[3-(2-hydroperoxy-3-methylbut-3-enyl)-2-hydroxy-4-methoxyphenyl]-3-(4-hydroxyphenyl)prop-2-en-1-one) (CID: 10022050)		-85.307	-89.316
K11	1-[4-(benzimidazol-1-yl)phenyl]-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (CID: 72678862)		-87.285	-83.732
K12	1-(3-bromo-2-hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (CID: 252077)		-72.607	-68.627
K13	(*E*)-1-[4-(4-methylpiperazin-1-yl)phenyl]-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (CID: 60195331)		-90.911	-88.510

K14	(*E*)-3-(2-chloroquinolin-3-yl)-1-(2,3,4-trichlorophenyl)prop-2-en-1-one (CID: 122188343)		-80.836	-78.672
K15	*N*-[3-[(*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]phenyl]-4-methylbenzenesulfonamide (CID: 11611227)		-88.490	-87.175
K16	*N*-[4-[(*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]phenyl]-4-methylbenzenesulfonamide (CID: 11668680)		-90.229	-85.378
K17	(*E*)-1-[4-(benzotriazol-1-yl)phenyl]-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (CID: 60195332)		-86.202	-83.091
K18	(*E*)-3-(5-bromo-2-methoxyphenyl)-1-(2-hydroxy-6-phenylmethoxyphenyl)prop-2-en-1-one (CID: 71735015)		-84.678	-84.506
K19	(*E*)-3-[4-[2-(2-aminoethylamino)-2-(7-chloroquinolin-4-yl)acetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (CID: 86579276)		-95.492	-96.175

K20	(*E*)-3-[4-[2-(2-aminopropylamino)-2-(7-chloroquinolin-4-yl)acetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (CID: 86579279)		-95.269	-98.593
K21	(*E*)-3-[4-[2-(3-aminopropylamino)-2-(7-chloroquinolin-4-yl)acetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (CID: 86579277)		-100.030	**-10.647**
K22	(*E*)-3-[4-[2-(7-chloroquinolin-4-yl)-2-piperazin-1-ylacetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (CID: 86579326)		-93.862	-93.702
K23	(*E*)-3-[4-[2-(7-chloroquinolin-4-yl)-2-[3-(methylamino)propylamino]acetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (CID: 86579323)		-100.103	**-102.403**
K24	(*E*)-3-[4-[2-(4-aminobutylamino)-2-(7-chloroquinolin-4-yl)acetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (CID: 86579278)		-102.183	**-101.988**
K25	(*E*)-3-[4-[2-(6-aminohexylamino)-2-(7-chloroquinolin-4-yl)acetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (CID: 86579280)		-105.442	**-106.995**

K26	(6*E*)-6-[[4-[(7-chloroquinolin-4-yl)amino]anilino]methylidene]-4-[(*E*)-3-(4-methoxyphenyl)-3-oxoprop-1-enyl]-2-methylcyclohexa-2,4-dien-1-one (CID: 70693919)		-104.953	**-103.458**
K27	(*E*)-3-[4-[2-[3-[3-aminopropyl(methyl)amino]propylamino]-2-(7-chloroquinolin-4-yl)acetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (CID: 86579325)		**-109.041**	**-107.380**
K28	(*E*)-3-[4-[2-[2-[2-(2-aminoethoxy)ethoxy]ethylamino]-2-(7-chloroquinolin-4-yl)acetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2-en-1-one (CID: 86579324)		-103.482	**-106.604**
	Lopinavir (comparison ligand)		-108.619	-100.658
	N3 (*native ligand*)	-	-121.629	-
	O6K (*native ligand*)	-	-	-107.992

The molecular docking results showed that the docking scores for most of the chalcone-derived compounds tested in this study were higher than the docking scores for native ligands and Lopinavir (Table 3). K27 compound had a lower docking score than lopinavir at both 6LU7 and 6Y2F receptors. This result means that K27 has the potency to act as an inhibitor in the replication process of the SARS-CoV-2. virus(Arwansyah, Ambarsari, & Sumaryada, 2014). According to (Fukunishi, Yamashita, Mashimo, & Nakamura, 2018), docking score is equivalent to bond-free energy. The lower the docking score, the stronger and more stable the ligand-protein interaction (Adelina, 2014; Reiner et al., 2020). The interaction of compound K27 with 6LU7 and 6Y2F receptors was stronger and more stable than lopinavir's interaction with these two receptors. Therefore, it can be predicted that the 6LU7 and 6Y2F inhibitory activity of compound K27 are better than that of lopinavir.

Table 3. Interaction of native ligands, comparison ligands, and chalcone-derived compounds with 6LU7 and 6Y2F

Ligand	6LU7		6Y2F	
	Hydrogen Bond	Hydrophobic Bond	Hydrogen Bond	Hydrophobic Bond
N3 (native ligand)	Thr190 Glu166 Gln189 Cys145 Ser144 Leu141 Gly143	Ala191 Pro168 Met49 Met165 His41 Thr25	-	-
O3K (native ligand)	-	-	His164 Gly143 Glu166 Phe140	His41 Met165 Pro168
Lopinavir	Gly143 Gln189	His41 Met49 Leu167 Pro168	Gln189 Ser144 Gly143 Cyc145	Pro168 Met165 Met49 His41
K27	Glu166 Met49 Asp187 Tyr54 Ala191	Pro168	Gln192 Thr190 Phe140 Glu166	Met49 Pro168 Cys44

Four compounds (K21, K23, K24, K25, K26, and K28) also had a lower docking score than lopinavir when interacting with the 6Y2F receptor. This condition indicates that the six compounds can inhibit the viral replication process through the 6Y2F receptor because their interaction with the receptor is more stable than lopinavir.

The K27 compound interaction with The 6LU7's active site occurs through hydrogen bonds and hydrophobic interactions. The hydrogen bonds formed occur from the oxygen and nitrogen atoms in the K27 compound with amino acid residues Glu166, Met49, Asp187, Tyr54, and Ala191. Hydrogen bonding with the amino acid residue Glu166 occurs when the native ligand N3 interacts with 6LU7 (Choudhary et al., 2020). Hydrophobic interactions between K27 and 6LU7 occur at Pro168 and Ala191. These are the same amino acid residues when native ligand N3 interacts with 6LU7.

The interaction of compound K27 with the active site of the 6Y2F receptor through hydrogen bonds occurs at the amino acid residues Glu166, Phe140, Thr190, and Gln192. The amino acid residues Glu166 and Phe140 form hydrogen bonds with the native ligand O6K, but the distance between the atoms is more extensive than in K27. This result shows that the hydrogen bonds formed in O6K are weaker than in K27 (Remer & Jensen, 2000). Hydrophobic interactions also occur with the amino acid residues Cys44, Met49, and Pro168.

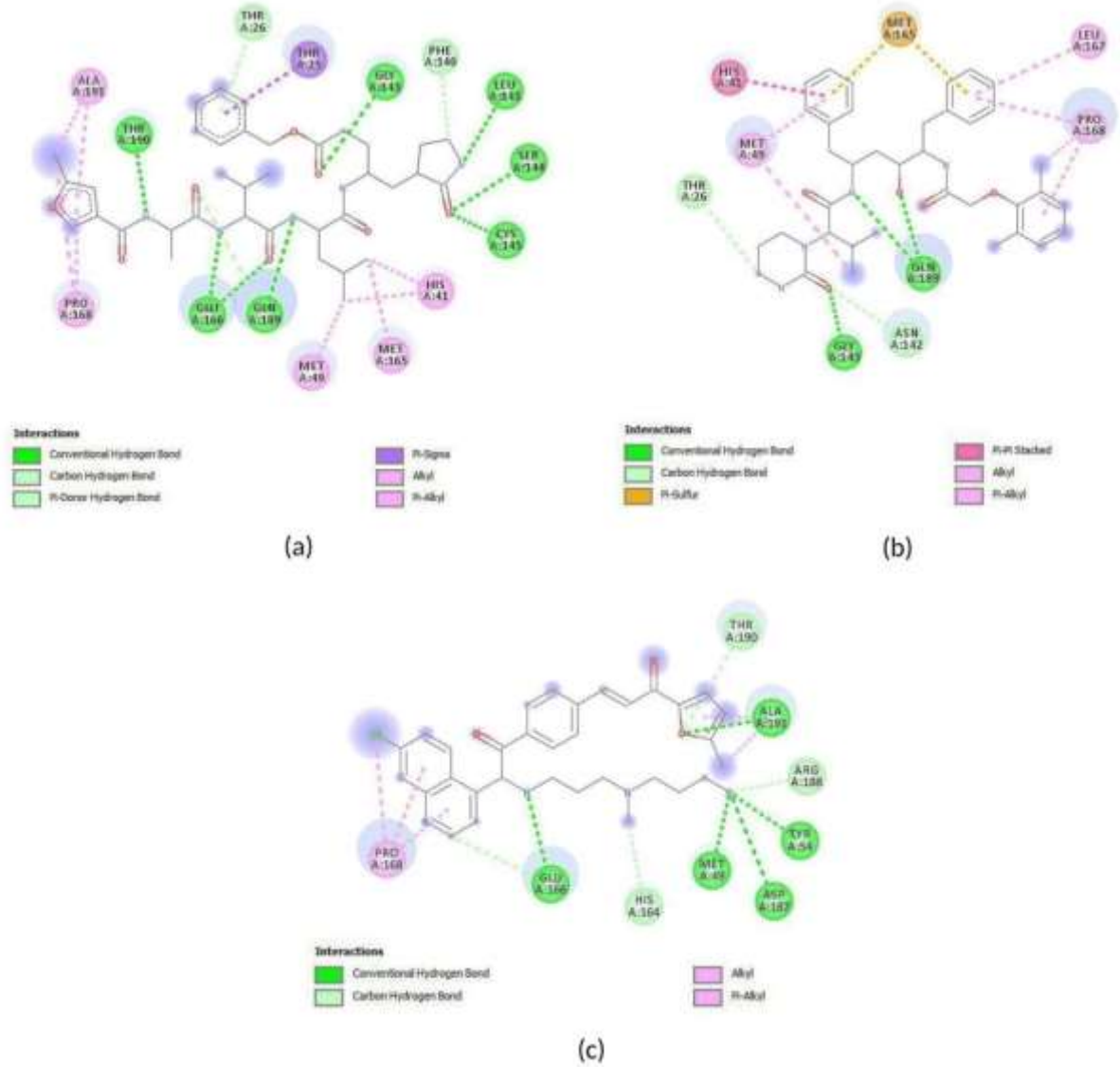


Figure 2. 2D interaction of native ligand (a), lopinavir (b), and K27 (c) with 6LU7 protein

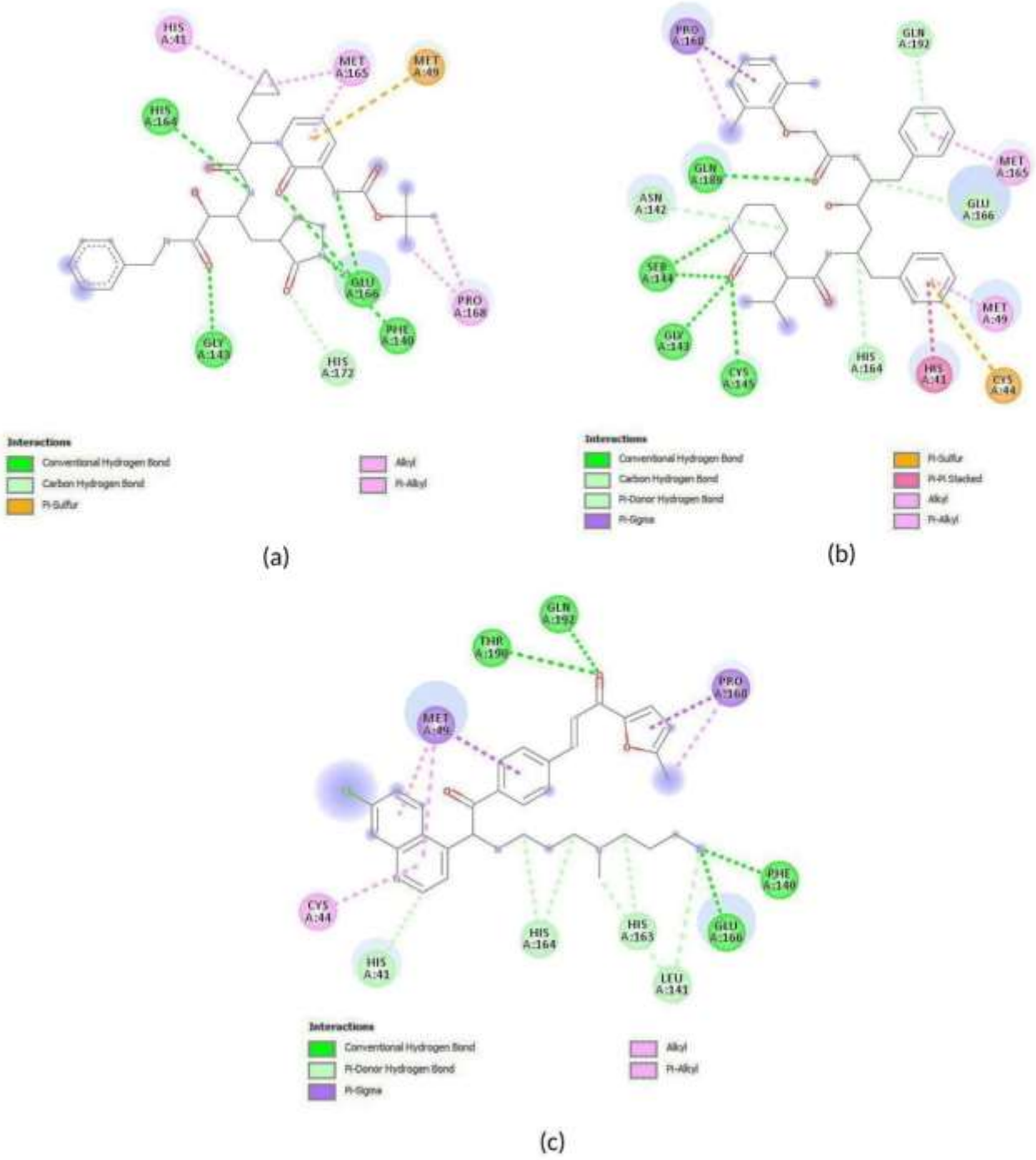


Figure 3. 2D interaction of native ligand (a), lopinavir (b), and K27 (c) with 6Y2F protein

CONCLUSION

Based on the molecular docking analysis results, it can be concluded that the K27 compound has the potential to inhibit the replication process of the SARS-CoV-2 virus through the mechanism of inhibition of the 6LU7 6Y2F receptors. Based on its docking score, its inhibitory activity is predicted to be better than lopinavir. The number of hydrogen bonds formed in the interaction of the K27 compound with 6LU7 is more than lopinavir-6LU7 interactions.

ACKNOWLEDGEMENT

The authors would like to thank the Dwi Puspita Education Foundation and LPPM Harapan Bangsa University for funding this research.

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