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Molecular Docking of Xanthone Derivatives as Therapeutic Agent for Covid-19**Emmy Yuanita^{1*}, Sudirman¹, Ni Komang Tri Dharmayani¹, Maria Ulfa¹,
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¹**ABSTRACT.** Covid-19 has caused more than 14 million confirmed cases and more than 6 hundred deaths as of 21 July 2020 globally. However, there is no approved drug to treat the disease. Xanthone is a potential therapeutic option for the virus that have been tested using molecular docking. There were 12 of xanthone compounds and its derivatives which have been docked against two protein crystals, 2GX4.pdb and 6FV1.pdb, which obtained two potential compounds of hydroxyxanthone derivatives with sulfonate and chloro substitution. These compounds are potentially developed into one of the agents for the treatment of infection COVID-19 disease. Based on energy data and interactions with amino acid residues when compared with its own native ligands, namely NOL and E8E, respectively. Energy docking and energy docking interactions are equal to - **43.3057** and - 45.5805 Kcal/mol respectively, during interactions with amino acid residues in the form of Gly 142, His 163, Cys144, Glu166, Gln164 and His 41. Based on these two data, it can be concluded that trihydroxyxanthone compounds **4** and **8** with chloro and sulfonate substitution are very potential to be developed as drug agents for Covid-19 disease therapy through protease inhibition.

Keywords: Binding, Docking, Covid_19, Inhibitor, Protease, Xanthone**INTRODUCTION**

Covid-19 is a new type of virus discovered in late 2019 and has never been identified in humans. This disease includes large families of Coronavirus (CoV), including Middle East respiratory syndrome CoV (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV). As a new type of virus, COVID-10 is a new problem for the world, based on WHO daily data, there have been 14,562,550 confirmed cases of Covid-19, including 607,781 deaths in 21 July 2020 (WHO, 2020). Therefore, WHO declare 2020 as a Covid-19 pandemic after the SARS-CoV pandemic in 2002 and MERS-CoV in 2012. Currently, there is no specific treatment against the new virus. Therefore, identifying effective antiviral agents to combat the disease is urgently needed. Some antiviral drugs, such as ribavirin, interferon, lopinavir-ritonavir, and corticosteroids, have been tested in patients with SARS or MERS, although the efficacy of some drugs remains controversial (Zumla, Chan, Azhar, Hui, & Yuen, 2016). Moreover, the latest research has revealed that remdesivir and chloroquine have effectiveness in inhibiting the recently emerged novel coronavirus in vitro. The EC90 value of remdesivir against Covid-19 in Vero E6 cells was 1.76 μ M, and the EC90 value of chloroquine against the Covid_19 in Vero E6 cells was

6.90 μ m (Wang et al., 2020). Therefore, remdesivir has been retained as a promising antiviral drug against the mechanism which incorporates into nascent virus RNA chains and results in premature termination (Warren et al., 2016). Meanwhile, Chloroquine is known to block virus infection by increasing endosomal pH required for viruses/cell fusion, as well as to interfere with the glycosylation of cellular receptors of SARS-CoV (Vincent et al., 2005). One of the classes of antiviral drugs as Protease inhibitors (PIs) (Sencanski et al., 2020), and SARS coronavirus main protease dan spike protein in mechanism drugs activity. A novel coronavirus (2019-nCoV), which is closely related to severe acute respiratory syndrome CoV (SARS-CoV) (Zhou et al., 2020).

The lack of effective drug variations causes high rates of death, and the spread of this disease is also uncontrollable. Therefore, the existence of a new disease epidemic caused by covid-19 is encouraging researchers to make new drug discoveries for the treatment of CoV infections. The natural products compound in which has antiviral activity is xanthenes derivatives, such as the mangostin and gamma mangostin compounds have shown potential inhibitory activity against HIV-1 protease (Chen, Wan,

& Loh, 1996). The result of previous studies which showed the presence of SARS-CoV analogues with Covid-19 led to the need to study the possibility of xanthenes as one of the candidates for therapy of Covid-19 infections. One study that can be carried out is computationally, specifically molecular docking. Molecular docking of xanthone compounds in this study will be carried out on two proteins 2GX4.pdb with the crystal structure of SARS coronavirus 3CL protease (3CL pro) inhibitor complex, and 6FV1.pdb with the structure of human coronavirus NL63 plays protease in the complex. We selected 3CLpro which is the main protease of the virus, envelope anchored spike protein from virus and receptor binding domain of this protein, SARS-CoV-2 helicase, Nsp10/16 complex a nonstructural protein and a single strand or RNA binding protein as target because of their importance in viral life cycle (Wu et al., 2020).

EXPERIMENTAL SECTION

Docking Molecules

The docking calculations were started with preparing various types of ligands which are derivatives of xanthone compound. The three-dimensional protein structure, 3C-like protease crystal structure with the code 2GX4.pdb, and NL63 main protease with the code 6FV1.pdb, were obtained from the Databank Protein website (www.pdb.org). Protease inhibitors were preventing viral replication by selectively binding to viral proteases and also blocking proteolytic cleavage of protein precursors which were necessary for the production of infectious viral particles. Docking in computational mechanism or theory is often equated with the term Lock and Key, where the conformation process of ligands and proteins does not change while forming bonds between ligands and proteins.

Preparation of Target Protein

Protein preparation was started by selecting the type and taking the protein data bank (2GX4.pdb and 6FV1.pdb) followed by the selection of one of the chains in the protein target and was finished by cleaning the protein from the residue. This process completed using Chimera® 1.1 software. The residue was removed, such as the H₂O molecule and the original ligand found in the protein crystal. After the protein target was free of residue, the second preparation stage was continued using Discovery studio® 3xx.1 software. This second preparation aimed to add hydrogen atoms; added atomic charges; and repaired the bonding of atoms damaged by the release of the original ligand.

Ligand Preparation

Ligands that used in docking were xanthone derivative compounds which have been successfully synthesized (Table 1). The preparation step was done by adding a charge on each constituent atom of ligand, adding hydrogen atoms to the ligand, and by minimizing energy. This ligand preparation was

performed using Discovery studio® 3.1 software. This preparation was done to get the most stable ligand conformation.

Docking Process

Molecular docking calculations were carried out using Discovery studio® 3.1 software. The first step was to form coordinates (grid) which were the place of docking between proteins and ligands. Docking coordinates were about about 9-10 Å made by copying the original ligand and pasting it to the prepared protein, then selecting the grid menu, and then the docking coordinates be formed automatically.

The docking process was first performed on the original ligand with a value of Root Mean Square Deviation (RMSD) smaller than 2 Å. This has a function to define a valid docking method to be used. If these requirements were met, then docking the recommended compound with the target protein had to be done. In the process of docking the target, protein is made rigid while the ligand is made flexible to bind to the active site of the protein.

Docking Analysis

The results of the docking process were opened using the Discovery studio 4.5 visualizer software. The ligand interaction menu was selected, then automatically the energy and binding site between the ligand and amino acid will appear. Interactions that generated can be hydrogen bonds and phi bonds. Each bond was distinguished from the colour of the bonds formed. Hydrogen bonds were usually green, while phi bonds were pink. Meanwhile, in Discovery Studio, the energy binding between the ligand and protein can be seen in the form of energy cDOCKER. The smaller the energy produced, the more stable the bond that occurs between the ligand and protein.

RESULTS AND DISCUSSION

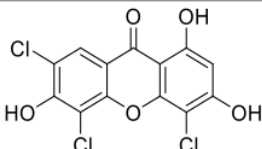
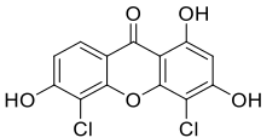
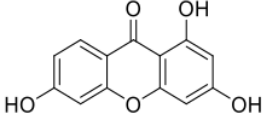
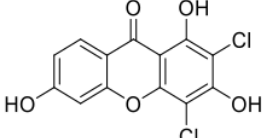
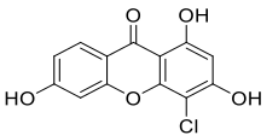
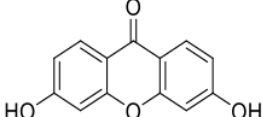
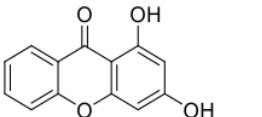
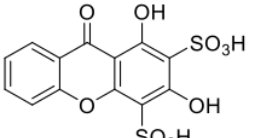
Molecular docking of xanthone compounds number one through twelve was examined on 3C-like proteases with the code 2GX4.pdb (original NOL ligand) and the main protease NL63 with code 6FV1.pdb (E8E, GOL, DMS, and original SO4). Both of these crystal structures of proteins belong to the protease inhibitor group, which is known as one of the antiviral treatments, including the coronavirus group (6,9). Molecular docking is used to obtain ligand interaction with amino acid residues from the protein used. This interaction will produce total bonding energy or also known as cDOCKER energy in terms of Discovery studio®. The smaller the energy produced, the more stable the protein-ligand bonds are formed. Another parameter is determined based on the distance of the bonds formed; the shorter the ligand-protein bonds formed, the more stable the ligand in which it binds to the active protein side of the target, therefore the energy is also smaller.

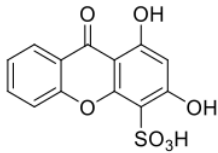
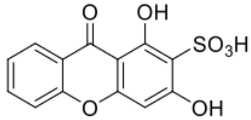
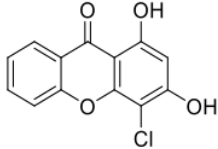
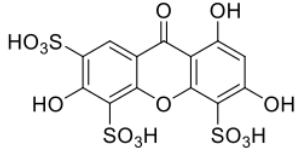
In this study, besides analyzed the docking of the original ligand-protein, docking was also carried out

on xanthone compounds which replace the ligand. Xanthone that used is that have been successfully synthesized in previous studies such as a series of hydroxyxanthone compounds as antioxidants (Yuanita et al., 2018), hydroxyxanthone compounds substituted

with chlorine (Miladiyah et al., 2020; Yuanita et al., 2019), the hydroxyxanthone series is antimalarial (Syahri et al., 2017), and the xanthone compound as an antibiotic (Yuanita et al., 2020), as shown in **Table 1**.

Table 1. Series of xanthone derivatives

Compound	Name	Structure	Reference
1	4,5,7-trichloro-1,3,6-trihydroxy-9H-xanthen-9-one		(Wu et al., 2020; Yang et al., 2006)
2	4,5-dichloro-1,3,6-trihydroxy-9H-xanthen-9-one		
3	1,3,6-trihydroxy-9H-xanthen-9-one		(WHO, 2020; Yang et al., 2006)
4	2,4-dichloro-1,3,6-trihydroxy-9H-xanthen-9-one		
5	4-chloro-1,3,6-trihydroxy-9H-xanthen-9-one		
6	3,6-dihydroxy-9H-xanthen-9-one		(WHO, 2020; Yang et al., 2006)
7	1,3-dihydroxy-9H-xanthen-9-one		(WHO, 2020; Yang et al., 2006)
8	1,3-dihydroxy-9-oxo-9H-xanthen-2,4-disulfonic acid		

9	1,3-dihydroxy-9-oxo-9H-xanthene-4-sulfonic acid	
10	1,3-dihydroxy-9-oxo-9H-xanthene-2-sulfonic acid	
11	4-chloro-1,3-dihydroxy-9H-xanthene-9-one	
12	3,6,8-trihydroxy-9-oxo-9H-xanthene-2,4,5-trisulfonic acid	

According to the analysis of eDOCKER energy and binding interaction (**Table 2** and **Table 3**), the lowest energy of bonding interaction obtained from the 12 derivatives of xanthone tested were compounds 1, 4, 8, 9, 10, and 12. These results suggested that xanthone compounds with chloro and sulfonate substitution have the best activity in inhibiting COVID-19 through inhibition of 2GX4.pdb proteases. As it known 2GX4.pdb is a crystal structure of SARS coronavirus 3CL protease. Furthermore, the interaction of native ligands such as Cln189; His41,

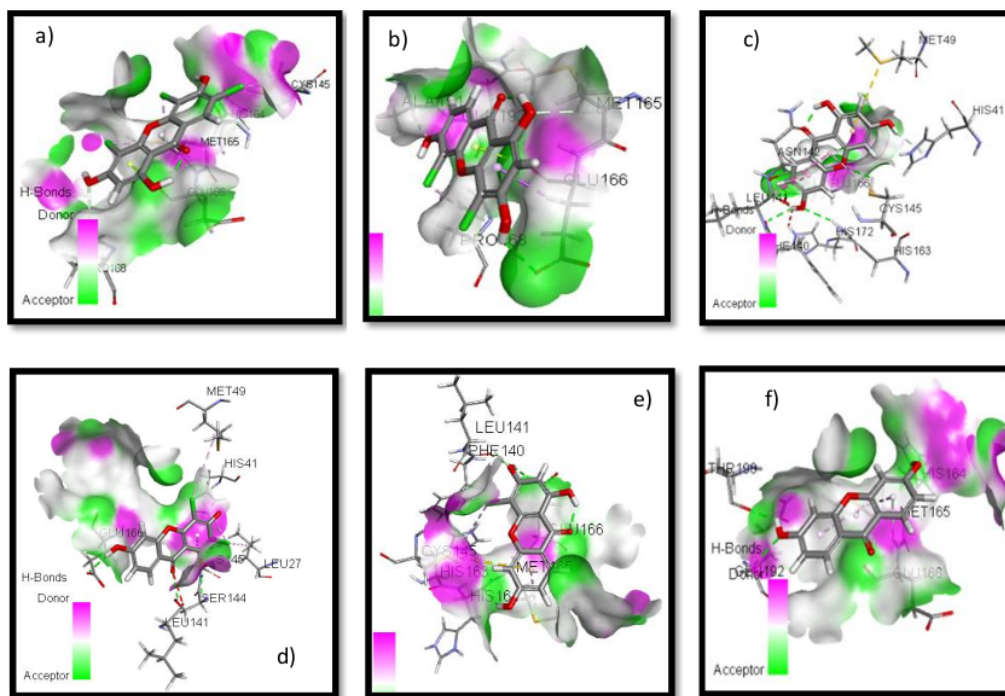
His 163; Glu166; Phe140 and Gly143 (Zhang et al., 2020), which is an inhibitor of Mpro SARS analogous to COVID-19, have similarities with amino acid residue interaction of compounds 1, 4, 8, 9, 10, and 12. The difference in the binding affinity value of each compound is influenced by the bonds formed, hydrogen bonds have an important role in determining the size of the binding value of affinity resulting from the docking process because it has higher energy than hydrophobic bonds.

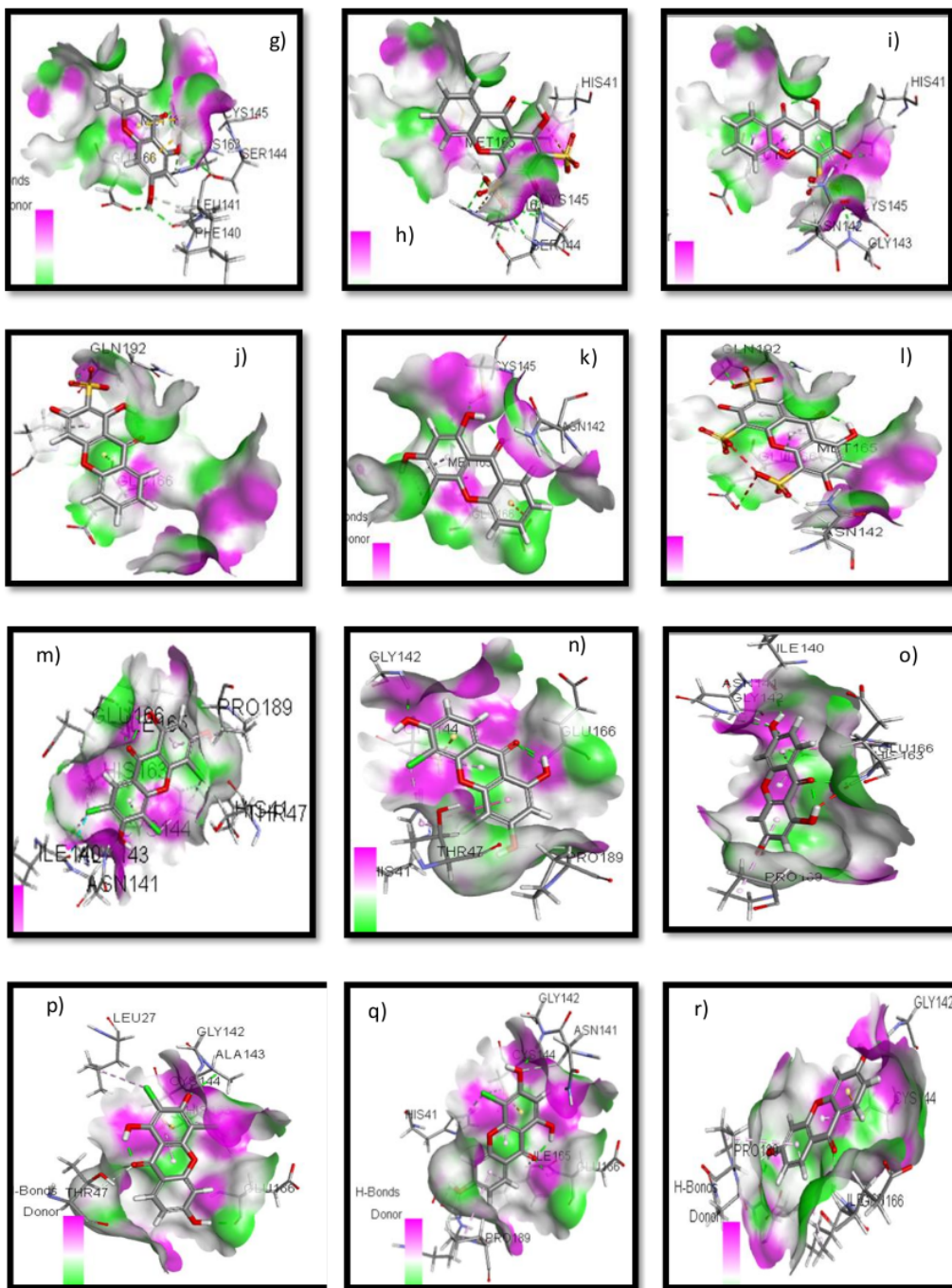
Table 2. cDOCKER energy of hydroxyxanthone derivatives to 2GX4.pdb and 6FV1.pdb

Compound	cDOCKER Energy (-kcal/mol)	
	6FV1.pdb	2GX4.pdb
1	29.146	36.5395
2	26.4584	31.2824
3	27.5714	31.291
4	31.1068	43.3057
5	28.9049	34.7324
6	25.0596	30.6685
7	27.9846	29.8673
8	32.4101	45.5804
9	28.4006	41.928
10	24.761	41.5818
11	22.9765	30.7725
12	32.5155	40.7307

Table 3. Binding interaction (amino acid residue) of hidroxyxanthone derivatives to 2GX4.pdb and 6FV1.pdb

Compound	Binding Interaction	
	6FV1.pdb	2GX4.pdb
1	Cys145, His164, Met165, Glu166, Pro168	Ile140, Ala143, Asn141, His163, Cys144, His41, Thr47, Ile165, Pro189, Glu166
2	Met165, Ala191, Pro168, Glu192, Glu166	Glu166, Cys144, Gly142, His41, Thr47, Pro189
3	Met49, His41, Cys145, His163, His172, Phe140, Glu166, Leu141	Pro189, Glu166, His163, Ile140, Asn141, Gly142, Cys144
4	Leu141, Ser144, Cys145, Leu27, His41, Met49, Glu166	Glu166, His163, Cys144, Leu27, Ala143, Gly142
5	Met165, Cys145, His164, His163, Leu141, Phe140, Glu166	Glu166, Ile165, Pro189, Gln188, Asp187, His41, Asn141, Gly142, Cys144
6	Gln192, Thr190, Met165, His164, Glu166	Glu166, Ile165, Cys144, Gly142, Asp187, Pro189, Gln188
7	Met165, Cys145, His163, Ser144, Leu141, Phe140, Glu166	Gln164, Ile165, Glu166, Ala143, Gly142, Cys144, Asn141
8	His41, Gly143, His163, Cys145, Met165, Ser144	His41, Cys144, Gly142, Ala143, Asn141, His163, Glu166, Ile165, Pro189
9	His41, Cys145, Asn142, Gly143, Glu166	Glu166, Ile165, His163, Cys144, Ala143, Asn141, Gly142, His41
10	Gln192, Pro168, Glu166	Pro189, Ile165, Glu166, Ala143, Asn141, Gly142, His163, Cys144
11	Asn142, Cys145, Met165, Glu166	Ile165, Glu166, Cys144, Gly142, His41, Pro189
12	Gln192, Glu166, Met165, Asn142	Gly142, Ala143, Cys144, His163, Asn141, Glu166





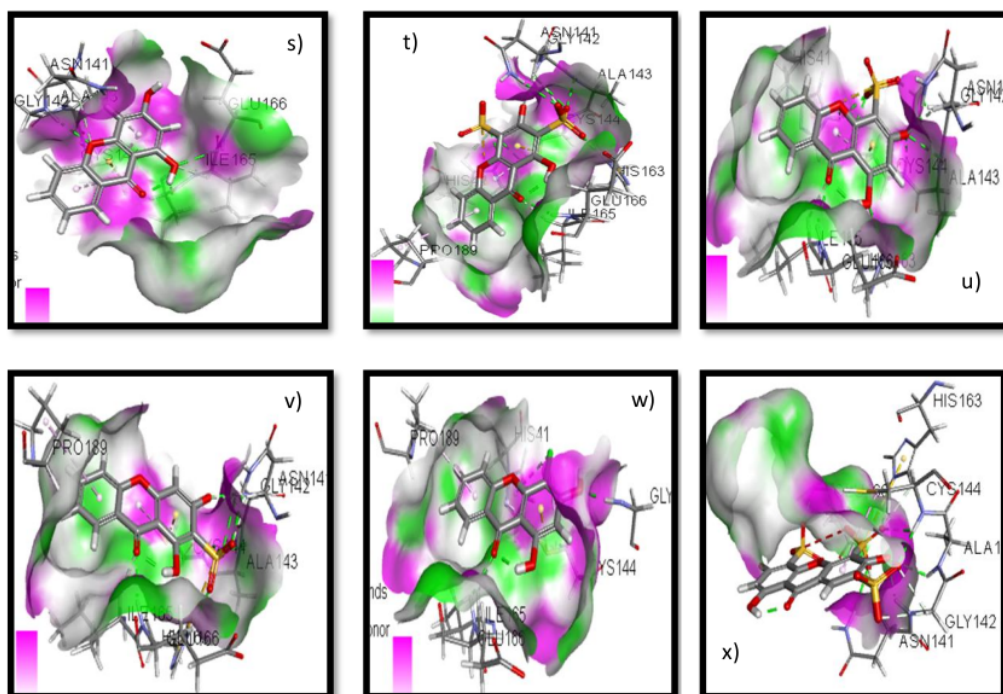


Figure 1. Best docked poses for tested xanthenes (1-12) a-l to 2GX4.pdb and m-x to 6FV1.pdb

Furthermore, interaction and energy that exhibited from xanthone compounds 1,4,8 and 12, namely trihydroxanthone groups with chloro and sulfonate substituents also have displayed the same result with human coronavirus in which represented by crystal protein 6FV1.pdb. The structure of human coronavirus NL63 main protease in the complex has native E8E ligand that interacts with amino acid residues of Gly 142, His 163, Cys144, Glu166; Gln164 and His 41. Even though the coronavirus has a diversity of species, but genomically the virus has similar essential elements that can be used as one of its treatment targets. As happened in the process of replication, the polyprotein 3C-Like protein (3CLpro), particularly at the stage to produce non-structural proteins (NSPs) such as RNA-dependent RNA polymerase (RdRp) and helicase, which are involved in the transcription and replication of the virus (Boheemen, Graaf, & Lauber, 2013), numerous enzyme inhibitor targeting these proteins have shown anti coronavirus activity in vitro. Another target is the surface structural spike glycoprotein which in this case is a principal element of activity (HCoV) – NL63) (Hofmann et al., 2005)

Based on these binding interaction and energy docking, it exhibited that hydroxyxanthone compounds with chloro and sulfonate substitution have the potential to be developed as the drugs target for SARS-CoV-2 therapy, especially on S protein. The spike protein (S-protein) performs two primary tasks that aid

in host infection: 1) mediates the attachment between the virus and host cell surface receptors, and 2) facilitates viral entry into the host cell by assisting in the fusion of the viral and host cell membranes (Yang et al., 2006). The target of this protein spike indicates the sulfonate-substituted hydroxyxanthone derivatives have prospect as a drug candidate for COVID-19 therapy at an early stage through the mechanism of preventing the virus from reaching the host cells.

CONCLUSIONS

In this study, docking studies were conducted on 12 hydroxyxanthone compounds in which known have antiviral activities, and as a result it is found that hydroxyxanthone with chloro and sulfonate substitution (4 and 8) may be used as drug therapies for the spread of coronavirus in the future. This is indicated based on these binding interaction and energy docking.

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REFERENCES

- Boheemen, S. Van, Graaf, M. De, & Lauber, C. (2013). *Syndrome in Humans Genomic Characterization of a Newly Discovered Coronavirus*. 3(6), 1–9. <https://doi.org/10.1128/mBio.00473-12>. Editor
- Chen, S. X., Wan, M., & Loh, B. N. (1996). Active constituents against HIV-1 protease from *Garcinia mangostana*. *Planta Medica*, 62(4), 381–382. <https://doi.org/10.1055/s-2006-957916>
- Hofmann, H., Pirc, K., Van Der Hoek, L., Geier, M., Berkhout, B., & Pöhlmann, S. (2005). Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. *Proceedings of the National Academy of Sciences of the United States of America*, 102(22), 7988–7993. <https://doi.org/10.1073/pnas.0409465102>
- Miladiyah, I., Yuanita, E., Nuryadi, S., Jumina, J., Haryana, S. M., & Mustofa, M. (2020). Synergistic Effect of 1,3,6-Trihydroxy-4,5,7-Trichloroxanthone in Combination with Doxorubicin on B-Cell Lymphoma Cells and Its Mechanism of Action Through Molecular Docking. *Current Therapeutic Research - Clinical and Experimental*, 92, 100576. <https://doi.org/10.1016/j.curtheres.2020.100576>
- Sencanski, M., Perovic, V., Pajovic, S. B., Adzic, M., Paessler, S., & Glisic, S. (2020). Drug Repurposing for Candidate SARS-CoV-2 Main Protease Inhibitors by a Novel in Silico Method. *Molecules*, 25(17). <https://doi.org/10.3390/molecules25173830>
- Syahri, J., Yuanita, E., Nurohmah, B. A., Wathon, M. H., Syafri, R., Armunanto, R., & Purwono, B. (2017). Xanthone as antimalarial: QSAR analysis, synthesis, molecular docking and in-vitro antimalarial evaluation. *Oriental Journal of Chemistry*, 33(1), 29–40. <https://doi.org/10.13005/ojc/330104>
- Vincent, M. J., Bergeron, E., Benjannet, S., Erickson, B. R., Rollin, P. E., Ksiazek, T. G., Seidah, N. G., & Nichol, S. T. (2005). Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virology Journal*, 2, 1–10. <https://doi.org/10.1186/1743-422X-2-69>
- Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*, 30(3), 269–271. <https://doi.org/10.1038/s41422-020-0282-0>
- Warren, T. K., Jordan, R., Lo, M. K., Ray, A. S., Mackman, R. L., Soloveva, V., Siegel, D., Perron, M., Bannister, R., Hui, H. C., Larson, N., Strickley, R., Wells, J., Stuthman, K. S., Van Tongeren, S. A., Garza, N. L., Donnelly, G., Shurtleff, A. C., Retterer, C. J., Gharaibeh, D., Zamani, R., Kenny, T., Eaton, B. P., Grimes, E., Welch, L. S., Gomba, L., Wilhelmsen, C. L., Nichols, D. K., Nuss, J. E., Nagle, E. R., Kugelman, J. R., Palacios, G., Doerfler, E., Neville, S., Carra, E., Clarke, M. O., Zhang, L., Lew, W., Ross, B., Wang, Q., Chun, K., Wolfe, L., Babusis, D., Park, Y., Stray, K. M., Trancheva, I., Feng, J. Y., Barauskas, O., Xu, Y., Wong, P., Braun, M. R., Flint, M., McMullan, L. K., Chen, S. S., Fearn, R., Swaminathan, S., Mayers, D. L., Spiropoulou, C. F., Lee, W. A., Nichol, S. T., Cihlar, T., Bavari, S. (2016). Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*, 531(7594), 381–385. <https://doi.org/10.1038/nature17180>
- World Health Organization. (2020). WHO coronavirus (COVID-19) dashboard. Retrieved from <https://covid19.who.int/>
- Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X., Zheng, M., Chen, L., Li, H. (2020). Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B*, 10(5), 766–788. <https://doi.org/10.1016/j.apsb.2020.02.008>
- Yang, S., Chen, S. J., Hsu, M. F., Wu, J. D., Tseng, C. T. K., Liu, Y. F., Chen, H. C., Kuo, C. W., Wu, C. S., Chang, L. W., Chen, W. C., Liao, S. Y., Chang, T. Y., Hung, H. H., Shr, H. L., Liu, C. Y., Huang, Y. A., Chang, L. Y., Hsu, J. C., Peters, C. J., Wang, A. H. J., Hsu, M. C. (2006). Synthesis, crystal structure, structure-activity relationships, and antiviral activity of a potent SARS coronavirus 3CL protease inhibitor. *Journal of Medicinal Chemistry*, 49(16), 4971–4980. <https://doi.org/10.1021/jm0603926>
- Yuanita, E., Pranowo, H. D., Mustofa, M., Swasono, R. T., Syahri, J., & Jumina, J. (2019). Synthesis, characterization and molecular docking of chloro-substituted hydroxyxanthone derivatives. *Chemistry Journal of Moldova*, 14(1), 68–76. <https://doi.org/10.19261/cjm.2018.520>
- Yuanita, E., Pranowo, H. D., Siswanta, D., Swasono, R. T., Mustofa, Zulkarnain, A. K., Syahri, J., Jumina. (2018). One-pot synthesis, antioxidant activity and toxicity evaluation of some hydroxyxanthones. *Chemistry and Chemical Technology*, 12(3), 290–295. <https://doi.org/10.23939/chct12.03.290>
- Yuanita, E., Sudarma, I. M., Sudewiningsih, N. M., Syahri, J., Dharmayani, N. K. T., Sudirman, Ulfa, M., Sumarlan, I. (2020). Antibacterial activity and molecular docking studies of series hydroxyxanthone. *AIP Conference Proceedings*, 2243(June). <https://doi.org/10.1063/5.0001090>

- Zhang, L., Lin, D., Kusov, Y., Nian, Y., Ma, Q., Wang, J., Von Brunn, A., Leyssen, P., Lanko, K., Neyts, J., De Wilde, A., Snijder, E. J., Liu, H., Hilgenfeld, R. (2020). α -Ketoamides as Broad-Spectrum Inhibitors of Coronavirus and Enterovirus Replication: Structure-Based Design, Synthesis, and Activity Assessment. *Journal of Medicinal Chemistry*, 63(9), 4562–4578. <https://doi.org/10.1021/acs.jmedchem.9b01828>
- Zhou, P., Yang, X. Lou, Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. D., Liu, M., Q., Chen, Y., Shen, X. R., Wang, X., Zheng, X. S., Zhao, K., Chen, Q. J., Deng, F. Liu, L. L., Yan, B, Zhan, F. X., Wang, Y. Y., Xiao, G. F., Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579(7798), 270–273. <https://doi.org/10.1038/s41586-020-2012-7>
- Zumla, A., Chan, J. F. W., Azhar, E. I., Hui, D. S. C., & Yuen, K. Y. (2016). Coronaviruses-drug discovery and therapeutic options. *Nature Reviews Drug Discovery*, 15(5), 327–347. <https://doi.org/10.1038/nrd.2015.37>

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