

PAPER • OPEN ACCESS

Molecular Docking of Quinine Derivative as Inhibitor in Sars-Cov-2

To cite this article: Destria Roza *et al* 2021 *J. Phys.: Conf. Ser.* **1819** 012053

View the [article online](#) for updates and enhancements.



240th ECS Meeting ORLANDO, FL

Orange County Convention Center Oct 10-14, 2021



Abstract submission due: April 9

SUBMIT NOW

Molecular Docking of Quinine Derivative as Inhibitor in Sars-Cov-2

Destria Roza^{1*}, Rini Selly¹, Rudi Munsirwan¹, Gianna Fadhilah²

¹Chemistry Department, Universitas Negeri Medan

²Biochemical Department, Institut Pertanian Bogor

* Correspondence author: destriaroza@unimed.ac.id

Abstract. The discovery of various of new medicinal compounds from various research clarifies the important role of computational studies as the initial basis for finding sources of medicinal raw materials both from natural and synthetic. SARS-coronavirus 2 (SARS-CoV-2) or COVID-19 is the virus which is responsible for the outbreak that affects almost the entire world began in early 2020. This study aim is to determine the interaction between SARS-CoV-2 and quinine derivative compounds by utilizing and developing quinine plants as medicinal ingredients, especially Corona antivirus. The research was conducted in silico with the molecular docking method. The docking software used in this research is AutodockVina. The results showed that from the 10 tested compounds against SARS-CoV-2 virus cells, all of it has the ability as an antivirus with the binding affinity of around -6 kcal / mol. The native ligands have the best binding affinity among the tested compounds which is around -7.9 kcal / mol. This is also supported by the number of hydrogen bondings and bond lengths as well.

1. Introduction

At the beginning of 2020, the world was startled by the outbreak of a new virus, namely Coronavirus. It is known that the origin of this virus came from Wuhan, China which was found at the first time in the end of December 2019. On February 11, 2020, the World Health Organization named the new virus as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and the disease name as Coronavirus disease 2019 (COVID-19). Coronavirus is a positive, encapsulated and unsegmented single-strain RNA virus. Coronavirus belongs to the order of Nidovirales, family of Coronaviridae. Coronaviridae are divided into two sub-families differentiated by serotype and genomic characteristics. There are four genus namely alpha coronavirus, betacoronavirus, deltacoronavirus and gamma coronavirus. [1-3]

Coronaviruses have capsules, particles that are spherical or elliptical, often pleomorphic with a diameter of about 50-200 nm. All viruses of the order Nidovirales are capsule, unsegmented, and RNA positive viruses also have very long RNA genomes. [3] The structure of the coronavirus forms a cube-like structure with the protein S located on the surface of the virus. Protein S or spike protein is one of the main antigen proteins of viruses and also the main structure for writing genes. This S protein plays a role in sticking and entry virus into the host cell (the interaction of S protein with its receptors in the host cell). The CoV spike (S) glycoprotein is the main target for vaccines, therapeutic antibodies, and diagnostics [3-4]



Wrapp determined the crystal structure of the SARS-CoV-2 S trimer using a 3.5 Å resolution cryo-electron microscope. The overall structure of SARS-CoV-2 resembles that of SARS-CoV S, with a root mean square deviation (RMSD) of 3.8 Å. One of the biggest differences between the two structures (although still relatively small) is the position of the RBD in their respective down conformations. [5] This information will support precision vaccine design and the discovery of antiviral therapy also accelerating treatment.

The main SARS-CoV-2 protease, Mpro, is a key enzyme that plays an important role in mediating viral replication and transcription. Dai (2020) designed and synthesized two lead compounds (11a and 11b) targeting Mpro. Both of them showed excellent inhibitory activity and strong anti-SARS-CoV-2 infectious activity. The X-ray crystalline structure of SARS-CoV-2 Mpro in a complex with 11a or 11b, both determined at a resolution of 1.5 Å indicates that the aldehyde groups 11a and 11b are covalently attached to Cys 145 Mpro. Both compounds show good pharmacokinetic properties in vivo, and 11a also shows low toxicity, which suggests that this compound is a promising drug candidate. [6].

The medical need to treat COVID-19 infection is of utmost importance. Chloroquine (CQ) has a strong antiviral effect on SARS-CoV infection in primate cells. This inhibitory effect observed when cells were treated, either before or after exposure to the virus, suggests prophylactic and therapeutic advantages. Despite the development in recent decades, CQ has never been chosen as a definite or effective treatment in humans, because it fails to translate in vitro efficacy into in vivo efficiency. Hydroxychloroquine and chloroquine (HCQ and CQ) have side effects especially on cardiac toxicity in patients. Well-designed clinical trials (randomized and controlled) are needed to clearly establish the safety and effectiveness of quinine derivatives such as Chloroquine as antiviral treatment. However, based on the risks and benefits that are still beneficial, CQ / HCQ could be part of the pharmacological weapon in the fight against SARS-CoV-2. [7-11]

HCQ and CQ is a derivative of quinine (Qn) and has a similar chemical structure. Qn has been known for hundreds of years as a medicine and as the prevention of malaria. If HCQ and CQ may help in treat or prevent COVID-19, for example quinine, which might taken as a tonic could become a benefit singly or multimodally to the world's population. Quinine was so bitter that British officials stationed in India and other tropical posts mixed the powder with soda and sugar. To meet the demands of British citizens abroad who need quinine to prevent malaria, the Schweppes Company of Geneva launched a commercial version, known as "Indian Quinine Tonic". Soon after, the British soldiers began mixing their daily tonic with lime and gin, which made the herbal concoctions even more palatable. According to Winston Churchill, "Gin and tonics saved more lives, and minds of the British people, than all the physicians in the Empire" [12]. Maybe taking tonic quinine (without gin) can help save more lives around the world, in this case, from 2019-nCoV? The risk of side effects from taking a controlled amount of quinine or quinine tonic appears to be low. There may be no, or little, harm in drinking a prophylactic dose of tonic water 3-4 ounces per day.

Analysis by Western, the stain of the virus in Vero B4 cells, showed that Quinine has antiviral activity against SARS-CoV-2, with 10 µM stronger than HCQ or CQ. The antiviral effect appears to be more specific, because in Vero cells, Qn affects cell viability approximately 50 times whereas HCQ and CQ therapy approximately 10 times. The data showed that Qn will have a potentially tolerable and widely used treatment option for SARS-CoV-2 infection, with a better predictable toxicology when compared to HCQ or CQ. In vitro observations on Qn showed a higher antiviral effect than HCQ or CQ, natural products can replace HCQ or CQ for the treatment of COVID-19 patients because the toxicity profile is quite good. Several in-vitro studies related, editorial, and expert consensus papers on quinine analogue antiviral treatment papers and historical treatises have been published. In March 2020 while the outbreak was unfolding in China, it was reported that the CQ drug had proven efficacy for COVID-19 pneumonia. [13-14]

The uses of computers in the discovery of new drugs aims to increase the efficiency of the simulation and calculation processes in drug design. Computers offer the in silico method as a complement to the in vitro and in vivo methods commonly used in drug discovery processes. This

approach was chosen because it requires fast time and lower costs. [15]. The purpose of this study was to analyze quinine derivatives against the SARS-CoV-2 receptor. The quinine derivatives used were the semi-synthesized quinine derivatives by Berghuis in unpublished research.

2. Research Methods

The materials used in this study are experimental data from the X-Ray Diffraction results from the SARS-CoV-2 receptor which can be downloaded in the protein data bank (PDB) <http://www.rcsb.org/pdb> with code 6m0k and 6svb. [5-6] The inhibitor compound, namely QN, CQN was taken from <https://pubchem.ncbi.nlm.nih.gov>. For Quinin derivatives, QN compounds were modified using Avogadro software based on the semi-synthesis data of quinine derivatives by Beurguis in an unpublished dissertation research. Quinine derivatives used as ligands include Quinine-N-Oxide, Quinine-di-N-Oxide, (Z) -8-ethylidene-2- (6-Methoxyquinoline 4-Carbonil) Quinclidine 1-Oxide, Quinine-9- Oxime, and 6- Methoxyquinoline -4-Carbonitrile, Quinine-9-on, Cichonidine-9-on [16-17]

Hardware consists of a computer with 8 GB RAM specifications, Quad Core Processor (Intel Core i3), Microsoft Windows 10 Pro 4.04 operating system. The software used for the docking simulation process is AutoDockTools-1.5.6 and AutoDock_vina 1_1_2. The preparation and analysis of the simulation results were carried out using the Discovery Studio and Pymol programs.

3. Results and Discussion

The validation of the method was carried out by redocking the ligand-free protein with the native ligand that had been previously separated using AutoDockTools-1.5.6. The parameter of the method validation is the value of RMSD (Root Mean Square Deviation). RMSD showed the degree of deviation from experimental ligand docking results to crystallographic ligands at the same binding site. The greater the RMSD value, the greater the deviation which indicates the greater the prediction error of ligand-protein interactions. A molecular docking method is said to be valid if it has an RMSD value $\leq 3 \text{ \AA}$ [18]. The smaller the RMSD value shows the better conformation because the position of the redocking ligand is closer to the ligand position resulted from the crystallography [19].

Based on the results obtained from 6m0k receptor with the Native ligand Molecule 3 is {N} - [(2 {S}) - 3- (3-fluorophenyl) -1-oxidanylidene-1 - [(2 {S}) - 1- oxidanylidene-3 - [(3 {S}) - 2-oxidanylidene-pyrrolidin-3-yl] propan-2-yl] amino] propan-2-yl] -1 {H} -indole-2-carboxamide (FJC) [6] an RMSD value is 1,309 Å. This analysis is valid, beside producing an RMSD value that is smaller than 3 Å, visualization of the docking validation results using Discovery Studio shows that the interaction between the receptor-ligand is in line with the hydrogen bonding interaction in the crystal structure. This hydrogen bonding is seen in between the ligand and the receptor on the acid residues GLY 143, CYS 145, CYS 145, HIS 163 and GLU 189 (Figure 1).

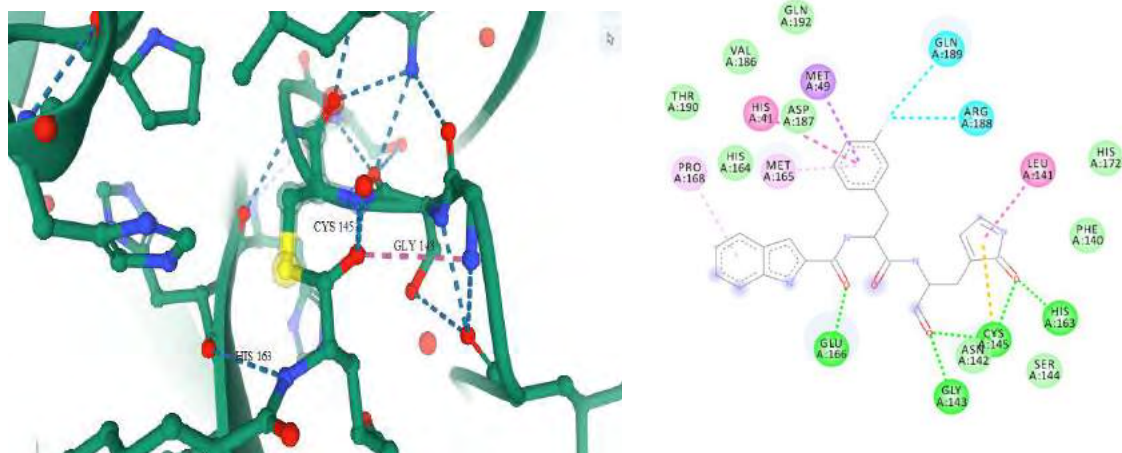


Figure 1. Receptor-ligand interaction between native ligand FJC with 6m0k (a) PDB crystal structure (b). docking results

The hydrogen bonding contributes to the affinity of a molecule for the target protein which forms electrostatic interactions (hydrogen donors and acceptors). Analysis of the hydrogen bonding interaction has the criteria of hydrogen bonding as a hydrogen donor and acceptor with a bond distance of 3.9 Å [19]. In the picture above, it shows the native ligand hydrogen bonding interactions involved with a bond distance smaller than 3.9 Å indicate a stable interaction.

Docking results for 10 chemical derivative test compounds. Based on the hydrogen bonding data obtained, the native ligand and 6m0k receptor have 5 hydrogen bondings and 8 hydrophobic bonds. The large number of hydrogen bondings determines the strength of the interaction, the native ligand has high stability, because it has a sufficiently large hydrogen bonding, that is 5 bonds, which can also be seen from the large free energy -7.9 kcal / mol (Table 1).

Table 1. Docking results using the SARS-CoV-2 Mpro receptor (6m0k)

No.	Quinine Derived Ligands	Bond Energy (kcal / mol)	Hydrogen bonds	Bond length (Å)	Number of bond < 5 Å
1	Native ligands	-7.9	GLY 143 CYS 145 CYS 145 HIS 163 GLU 189	1.84 3.25 3.54 2.12 3.19	13 (5 Hydrogen bondings and 8 hydrophobic bonds)
2	Chloroquine	-5.5	GLY 143 CYS 145 CYS 145 ASN 42	2.26 3.60 3.98 3.8	7 (4 Hydrogen bondings and 3 hydrophobic bonds)
3	Quinine	-6.2	HIS 164	3.71	4 (1 Hydrogen bonding and 3 hydrophobic bonds)
4	Cichonidine	-6.0	-	-	6 hydrophobic bonds
5	Quinine-N-Oxide	-6.3	-	-	4 hydrophobic bonds
6	Quinine-di-N-Oxide	-6.6	HIS 164 HIS 164	2.16 3.58	5 (2 Hydrogen bondings and 3 hydrophobic bonds)
7	(Z) -8-ethylidene-2- (6-Methoxyquinoline 4-Carbonyl) Quinclidine 1-Oxide	-6.6	HIS 163 Phe 140 GLU 166	1.93 3.45 3.64	7 (3 Hydrogen bondings and 4 hydrophobic bonds)
8	Quinine-9-Oxime	-6.1	HIS 164	3.45	8 (2 Hydrogen bondings and

9	6- Methoxyquinoline -4- Carbonitrile	-5.3	ASN 142 GLN 192	3.56 2.35	6 hydrophobic bonds) 4 (1 Hydrogen bonding and 3 hydrophobic bonds
10	Quinine-9-on	-6.3	GLN 189 PHE 140 GLU 166 CYS 145	3.39 3.58 3.51 4.13	6 (4 Hydrogen bondings 2 hydrophobic bonds)
11	Cichonidine-9-on	-6.4	HIS 41	3.55	3 (1 Hydrogen bonding 2 hydrophobic bond)

The docking results show that the quinine derivative has a fairly good energy (has a negative free energy value) but it is still bigger than the native ligand. Of the 10 ligand test compounds (Z) -8-ethyliden-2- (6-Methoxyquinoline 4-Carbonyl) Quinclidine 1-Oxide has a smaller free energy, about -6.6 kcal / mol. This is influenced by hydrophobic interactions which also play an important role in the stability of the ligands against the receptors. Hydrophobic interactions are interactions that avoid a liquid environment and tend to cluster on the inside of the globular protein structure to minimize interactions with water which can damage the protein structure and cause enzymes to lose their activity [20]

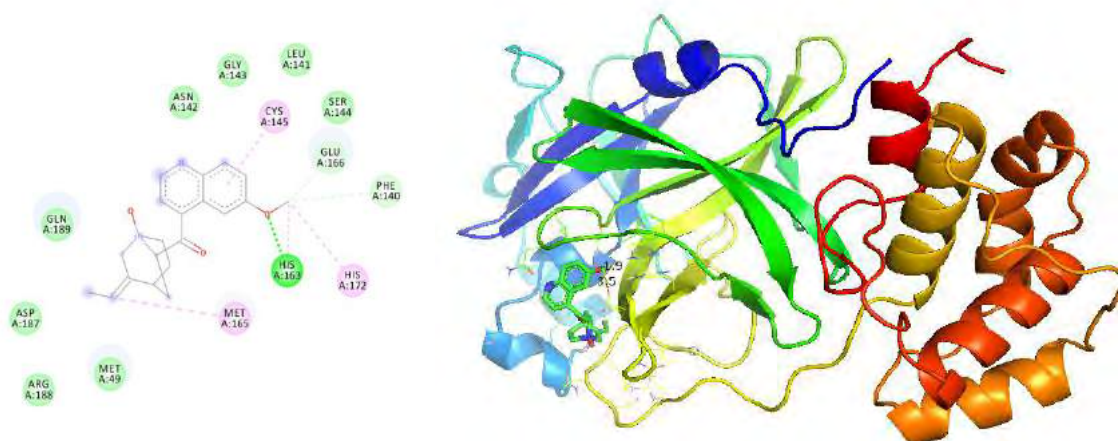


Figure 2. Visualization of docking results ligand (Z) -8-ethyliden-2- (6-Methoxyquinoline 4-Carbonyl) Quinclidine 1-Oxide with SARS-CoV-2 Mpro receptor (6m0K) (2D and 3D)

The docking process results between quinins and their derivatives with the receptors SARS-CoV-2 S protein with the code 6svb shows a fairly good energy, around -5.4 to -6.5 kcal / mol. The bond energy is smaller than the native ligand -2.6 kcal / mol. This shows that quinine stability is better. This is because the native ligand (2-acetomida-2-deoxy-beta-D-glucopyranose, NAG) in the crystals is scattered on each side of the receptor, whereas in the docking process only 1 native ligand molecule is used, in other words it is difficult to select the ligand that is right that interacts directly with the receptors. This result also supported with the RMSD value which is around 3,661 Å. However, the grid box parameter using this ligand was quite successful on quinine test compounds and their derivatives. It can be seen that these molecules can still form hydrogen bondings with the active side of the target proteins and the resulting bond energy is negative. Likewise, using the native FJC ligand provides the best energy value, close to the energy with the Mpro receptor.

Table 2.Docking results using the SARS-CoV-2 (S) protein receptor (6vsb)

No.	Quinine Ligands	Derivative	Bond Energy (kcal / mol)	Hydogen Bonding	Bond length (Å)	Number of bond<5Å
1	Native ligand 1 (FJC)		-7.0	ASN A: 709 ASN A: 709	1.96 2.51	8 (2 Hydrogen bonding, 1 halogen bond, 1 pi-sulfur and 3 hydrophobic bonds)
2	Native ligands		-2.6	-	-	-
3	Chloroquine		-5.4	ASN A: 709 ASP B: 796 THR B: 1077	2.45 3.60 3.98	7 (2 Hydrogen bonding and 5 hydrophobic bonds)
4	Quinine		-5.7	ASP B: 796 ASP B: 796	3.38 3.42	4 (1 Hydrogen bonding and 3 hydrophobic bonds)
5	Cichonidine		-5.7	ASP B: 796 ASP B: 796 ASN A: 709	3.04 3.47 2.51	5 (3 hydrogen bondings and 2 hydrophobic bonds)
6	Quinine-N-Oxide		-5.7	ASN A: 709 ASN A: 709	2.46 3.18	6 (2 hydrogen bondings and 4 hydrophobic bonds)
7	Quinine-di-N-Oxide		-5.8	HIS 164 HIS 164	2.16 3.58	5 (2 Hydrogen bondings and 3 hydrophobic bonds)
8	(Z) -8-ethilliden-2- (6-Methoxyquinoline 4-Carbonil) Quinclidine 1-Oxide	(6-4-	-6.2	ASN A: 709 ASP B: 796	2,144 2.89	7 (2 Hydrogen bondings 1 electrostatic bond and 4 hydrophobic bonds)
9	Quinine-9-Oxime			HIS 164 ASN 142	3.45 3.56	8 (2 Hydrogen bondings and 6 hydrophobic bonds)
10	6- Methoxyquinoline -4- Carbonitrile		-6.5	TYR A: 707 Phe B: 898 ALA B: 899	2.72 2.63 2.69	6 (3 Hydrogen bondings and 3 hydrophobic bonds)
11	Quinine-9-on		-5.9	ASN A: 709	2.19	6 (1 Hydrogen bonding 5 hydrophobic bond)
12	Cichonidine-9-on		-5.8	ASN A: 709	2.26	3 (1 Hydrogen bonding 4 hydrophobic bond)

Like the Mpro receptor docking results from the ligand test compound (Z) -8-ethilliden-2- (6-Methoxyquinoline 4-Carbonil), Quinclidine 1-Oxide has a smaller free energy, around -6.2 kcal / mol. Apart from the effect of hydrogen bonding and hydrophobic interactions, there are also electrostatic interactions which are interactions between atoms caused by their polarity [21]. This interaction is a weak and non-covalent interaction so that it is easy to escape, but in large numbers, this interaction can have a big effect on stability [22]. Interactions between ligands and receptors generally occur at amino acid residues ASN A: 709, ASP B: 796, THR B: 1077, HIS 164, ASN 142, TYR A: 707, Phe B: 898, ALA B: 899 (figure 3).

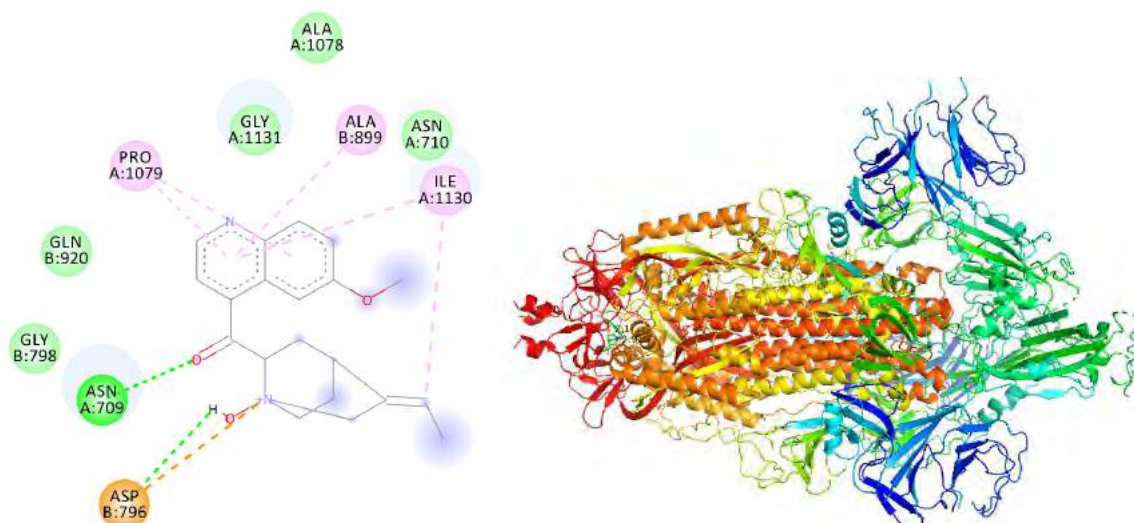


Figure 3. Visualization of docking results ligand (Z) -8-ethylidene-2-(6-Methoxyquinoline 4-Carbonyl) Quinclidine 1-Oxide with SARS-CoV-2 (S) receptor protein (6vsb)

4. Conclusion

Quinine derivative compounds have good stability to the SARS-CoV-2 receptor. This can be seen from the relatively low bond energies, which are around -5.4 to 6.6 kcal / mol. The interactions between ligands and receptors are seen in hydrogen bonding, hydrophobic interactions and electrostatic interactions are formed. So that quinine derivative compounds may be used as drug candidates for SARS-CoV-2.

Acknowledgments

The author would like to thank the funding assistance from Universitas Negeri Medan. I would also like to express my gratitude to the Dean and all academics of the Department of Chemistry, FMIPA Unimed.

References

- [1] WHO Novel Coronavirus (2019-nCoV) 2020 *Situation Report-1*
- [2] Huang C, Wang Y, Li X, Ren L, Zhao J, Zang Li, Fan G 2020 Clinical features of patients infected with the 2019 novel coronavirus in Wuhan China *The Lancet*
- [3] Wang Z, Qiang W, Ke H 2020 A Handbook of 2019-nCoV Pneumonia Control and Prevention *Hubei Science and Technologi Press China*
- [4] Fehr AR, Perlman S 2015 Coronavirus: An Overview of Their Replication and Pathogenesis *Methods in Molecular Biology* **128** 21–23
- [5] Wrapp D, Wang N., Corbett, KS, Goldsmith JA, Abiona O., Graham BS, McLellan JS 2020 Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation *Science* **367** 1260–1263 DOI: 10.2210 / pdb6vsb / pdb
- [6] Dai W, Zhang B, Jiang X, Su H, Li J., Zhao Y, Xie X, Jin Z, Peng J, Liu F, Li C, You Li Y, Bai, F, Wang H, Cheng X, Cen X, Hu S, Yang Z, Wang J, Liu X, Xiao G, Jiang H, Rao Z, Zhang L, Xu Y, Yang H, Liu H 2020 Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease *Science* **368**(6497) 1331-1335 DOI: 10.1126 / science.abb4489
- [7] Oscanoa TJ, Romero-Ortuno R., Carvajal A., Savarino A., A pharmacological perspective of chloroquine in SARS-CoV-2 infection: An old drug for the fight against a new coronavirus

- ?, 2020, Elsevier BV and International Journal of Antimicrobial Agents **56**(3) 0924-8579 <https://doi.org/10.1016/j.ijantimicag.2020.106078>
- [8] Rebeaud ME, Zores F 2020 SARS-CoV-2 and the Use of Chloroquine as an Antiviral Treatment *Frontiers in Medicine* **7** 184. doi: 10.3389 / fmed.2020.00184
- [9] Smit C, Peeters MYM, Anker JN, Knibbe CAJ 2020 Chloroquine for SARS-CoV-2: Implications of Its Unique Pharmacokinetic and Safety Properties, *Clinical Pharmacokinetics* **59** 659–669 <https://doi.org/10.1007/s40262-020-00891-1>
- [10] Hoffmann M, Mösbauer K, Hofmann-Winkler H, Kaul A, Kleine-Weber H, Krüger N, Gassen NC, Müller MA, Drosten C, Pöhlmann S 2020 Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2 *Nature* **585**(7826)
- [11] 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 inhibited the recently emerged novel coronavirus (2019-nCoV) in vitro *Cell research* **30** (3) 269-271
- [12] Jomsky MJ, Kerna NA, 2020 Could Low-Dose Quinine Prevent or Treat Coronavirus Infection *EC Pharmacology and Toxicology* **8**(4)
- [13] Große M, Ruetalo N, Businger R, Rheber S, Setz C, Rauch P, Auth J, Brysch K, Schindler M, Schubert U, Evidence That Quinine Exhibits Antiviral Activity against SARS-CoV-2 In Vitro Infection *Communication* Not Peer-Reviewed
- [14] Inklebarger JIJ, Gyer GM, Galanis N, Ghulam A, Michael JM 2020 Cinchona Bark for the Treatment of Covid-19 Pneumonia: A Modern Review of the Potential Anti-Viral Therapeutic Applications of an Old Treatment *International Journal of Medical Science and Clinical Invention* **7**(5) 4795-4801 <https://doi.org/10.18535/ijmsci/v7i05.02>
- [15] Ekins S, Mestres J, Testa B 2002 In silico pharmacology for drug discovery: application to targets and beyond *British Journal of Pharmacology, Review* **152** 21-37.
- [16] Aisyah A, Berghuis NT, Santoso J, Syah YM, Mujahidin D 2014 Synthesis of quinine N-oxide and an NMR tutorial in its structure determination *Indonesian Journal of Tea and Cinchona Research* **17**(1) 11- 20 DOI: <https://doi.org/10.22302/pptk.jur.jptk.v17i1.45>
- [17] Berghuis, NT 2018 Synthesis of Quinine Alkaloid Derivatives and Their Antibacterial Activities *Dissertation* (Bandung: ITB)
- [18] Jain, AN and Nicholls A 2008 Recommendation for Evaluation of Computational Methods *Journal of Computer-Aided Molecular Design* **22** 133-139
- [19] Bissantz, C, Folkers G, and Rognan D 2000 Protein-Based Virtual Screening of Chemical Databases 1 Evaluation of Different Docking / Scoring Combinations *Journal of Medicinal Chemistry* **43** 4759-4767
- [20] Lins L, Brasseur R 1995 The hydrophobic effect in protein folding *Faseb J* **9** 535-540
- [21] Rajagukguk, J., Situmorang, R., Djamal, M., Rajaramakrishna, R., Kaewkhao, J. and Minh, P.H., 2019. Structural, spectroscopic and optical gain of Nd³⁺ doped fluorophosphate glasses for solid state laser application. *Journal of Luminescence*, **216**, p.116738.
- [22] Sharp KA, Honig B 1990 Electrostatic interactions in macromolecules: theory and Applications *Annu Rev Biophys Biophys Chem* **19** 301-322