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Molecular Docking Study for Prediction of Chiral HPLC Separation of Hydroxychloroquine as an Alternative Antiviral of SARS-CoV-2

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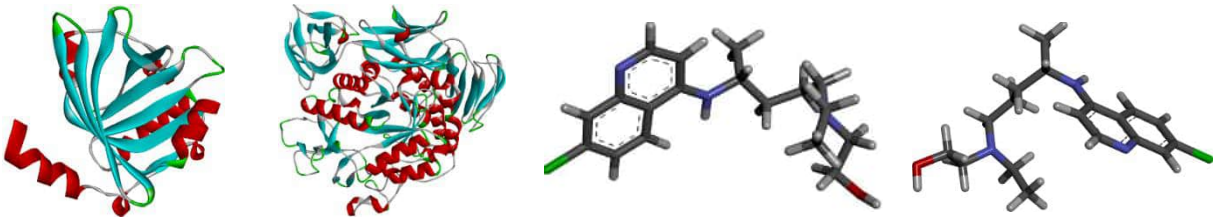
Abstract. The HPLC chiral separation of hydroxychloroquine (HCQ) using chiral α-1-acid glycoprotein (AGP) column has been predicted based on a molecular docking approach. The research was initiated with the geometrical optimization of the HCQ compound using the quantum calculation method of semiempirical (SE) of PM6, AM1, and PM3, and Hartree-Fock (HF) and density functional theory (DFT/B3LYP) with the basis set of 3-21G, 6-31G, and 6-311G. Molecular docking was performed with AutoDock Vina application on exhaustiveness of 264. Redocking with AutoDock Vina was done using coordinates of X = 13.584; Y = 1.47; Z = 18.451 with a grid box size of 40 x 40 x 40 and a grid Spacing of 0.375 Å, followed by specific docking process using the same conditions as redocking. The DFT method with the basis set of 6-311G was the best calculation method because it gives the lowest PRESS and closest r^2 value to one for the comparison between calculated and experimental data of ^{1}H-NMR. The docking result shows that R-HCQ enantiomer has more negative value of binding energy and more diverse interactions in the inclusion complex, indicating that R-HCQ forms more stable complex with AGP, and therefore it will be retained longer in the AGP column and eluted from the column later after R-HCQ.

Introduction

Since the first cases reported, the SARS-CoV-2 virus infection has become a pandemic [1]. There has been no specific treatment for the SARS CoV-2 virus [2]. Various outbreaks caused by viruses continue to emerge even though they are caused by many different types of viruses [3]. Several antivirals are used as alternatives to treat SARS-CoV-2, one of which is hydroxychloroquine (HCQ) [4]. Based on antiviral and prophylactic activities, the safety level of HCQ is considered better than chloroquine [5]. Antivirus is a drug that is specifically used for viral infections. The drugs used today are mostly chiral compounds [6]. The enantiomers in a chiral drug have identical physicochemical properties but can show differences in pharmacokinetics, pharmacodynamics, and toxicity [7]. Therefore, to enhance the drug efficacy, separation of enantiomers of the chiral drug is frequently needed [8]. One of the methods for chiral separation is by using HPLC [9]. However, separation of chiral drug is not easy, tedious and requires a certain eluent and/or chiral column which is relatively expensive. In addition, several optimizing steps that needs a lot of time and solvents should also be carried out before the enantiomers can completely be separated. Focusing on the concept of sustainable chemistry, molecular docking approach of enantiomers and the chiral column to predict the separation and mechanism of chiral compounds has been carried out [10]. In this study, molecular docking methods has been utilized to predict chiral separation of HCQ antiviral drugs by HPLC and to understand the separation interaction between R and S-HCQ with chiral column of α-1-acid glycoprotein (AGP).

Experimental Details

Materials. The crystal structure of the α-1-acid glycoprotein (AGP) column complex (as macromolecule) was taken from the Protein Data Bank (PDB id 3APW). The ligand used in this study was the optimized structure of hydroxychloroquine (HCQ), shown in Fig. 1.



(a) (b) (c) (d)

Figure 1. 3D crystal structure of (a) AGP; (b) β-CD; and the structure of (c) R- and (d) S-HCQ

Instrumentation. A personal computer with an Intel Core i3-7100, 3.90 GHz, 8 GB RAM capacity was used for geometry optimization. A laptop with an AMD A4-3330MX APU HD Graphics processor, 2.30 GHz, 2 GB RAM capacity was used for molecular docking. The enantiomeric structure of the chiral drug (as a ligand) was sketched by ChemDraw Professional 17.1. Geometry optimization was carried out with Gaussian® 09W and GaussView. Docking study was performed with AutoDock Viva. PyMOL was used to calculate the redocking RMSD value. Discovery Studio 2019 was used to visualize molecular docking results as well as ligand and macromolecular preparation.

Selection of the best calculation methods. The selection of appropriate computational methods was done to optimize the structure HCQ. Several calculations, including Semi-empirical (SE) of PM6, AM1, and PM3 as well as Hartree-Fock (HF) and Density functional theory (DFT/B3LYP), each with the basis set of 3-21G, 6-31G, and 6-311G were performed. The optimized structure of HCQ from each calculation was subjected to ^{1}H-NMR chemical shift (δ) calculation and the results were compared with experimental ^{1}H-NMR data reported by Dongre et al. [11]. The best calculation method was selected from the one that gave the smallest Prediction Error Sum of Squares (PRESS) value and the closest determination coefficient (r^2) value to 1 [12].

Geometry optimization. The geometry optimization of the R- and S-HCQ compounds was carried out using DFT 6-311G calculation method. The use of this calculation method was based on the result obtained from the previous step of calculation method selection.

Molecular docking with AutoDock Vina. The optimized R- and S-HCQ structure were used as starting conformation in the molecular docking. α-1-acid glycoprotein (AGP) was taken from the Protein Data Bank and prepared by Discovery Studio 2019 to separate macromolecules from native ligands and water molecules. Redocking of native ligand used coordinate value of X = 13.584; Y = 1.47; Z = 18.451 with a grid box size of 40 x 40 x 40 and a grid Spacing of 0.375 Å. The specific docking process used the same conditions as redocking. Docking was considered to be valid if it had a root mean square deviation (RMSD) < 2,000 Å [13]. Visualization of molecular docking results was done with Discovery Studio 2019.

Result and Discusion

Selection of the best calculation methods. The selection of the appropriate method is a necessary step in computational chemistry. It aims to select the best calculation method to be used. The best method must be able to describe the geometric structure of the compound most accurately. In this study, geometry optimization has been done on three quantum calculation methods, each with three basis sets, namely semi-empirical (SE) of PM6, AM1, and PM3 methods as well as Hartree Fock (HF) and density functional theory (DFT/B3LYP) with the basis set of 3-21G, 6-31G, and 6-311G. Chloroquine (CQ) has been used as a model for the selection of the appropriate method. CQ has been

chosen because it is the parent compound of HCQ. CQ has simpler structure than HCQ, with the difference between CQ and HCQ only in the hydroxyl group. In addition, ^{1}H-NMR data for CQ compounds are also available in the literature of Dongre et al. [11], so that it can be used as reference/experimental data. Fig. 2 presents the structure of the CQ compound and its labeling.

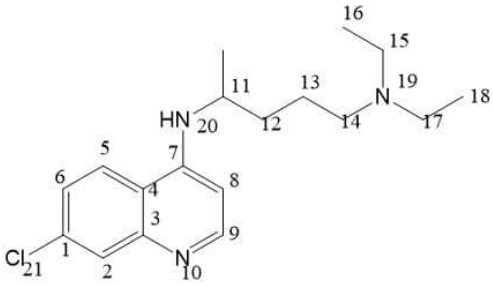


Figure 2. Structure of chloroquine compound and its numbering

Table 1 presents a summary of the PRESS and r^2 values for the comparison between experimental and calculated ^{1}H-NMR chemical shift of the optimized CQ using different quantum calculation methods.

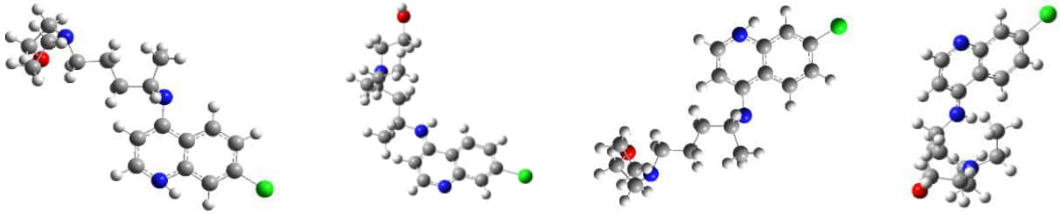
Table 1. The value of PRESS and r^2 from the comparison of the experimental chemical shift data with the results of calculations using various quantum calculation methods

Calculation methods	Basis sets	PRESS	r^2
Semi-empirical	PM-6	23.6547	0.5170
	AM-1	18.8576	0.9423
	PM-3	20.2647	0.9319
Ab Initio (Hartree-Fock)	3-21G	6.4702	0.9690
	6-31G	6.2367	0.9716
	6-311G	7.2808	0.9713
Density-functional theory	3-21G	8.4195	0.9544
	6-31G	5.7171	0.9690
	6-311G	5.0892	0.9695

Based on Table 1, it can be seen that DFT 6-311G is the best method in modeling CQ compounds among the other methods used, as evidenced by the smallest PRESS value and the closest r^2 value to 1. Therefore, the 6-311G DFT method is selected to be used in the geometry optimization the R- and S-HCQ compounds.

Geometry Optimization. Geometry optimization can describe the location of atoms in a stable molecular conformation with the lowest energy state [14]. That is a representation of the molecular structure adopted by the compound in nature. Geometry optimization on each compound of R- and S-HCQ has been done with DFT 6-311G. The conformations of the R- and S-HCQ compounds before and after geometry optimization with DFT 6-311G are presented in Fig 3.

Structure of HCQ shown in Fig. 3 indicates the change of geometric structure of R- and S-HCQ compounds before and after geometry optimization. Before optimization, the carbon chain geometry is described as straight, but after geometry optimization the carbon chain becomes bent. This is due to the repulsion between the nitrogen atom and the chiral part. In S-HCQ, nitrogen and chiral lies in one plane, this causes S-HCQ is more bent than R-HCQ.



(a) (b) (c) (d)

Figure 3. Structure of R-HCQ compound (a) before optimization, (b) after optimization and S-HCQ (c) before optimization, (d) after optimization using DFT 6-311G

Molecular docking of HCQ on AGP with AutoDock Vina. Molecular docking is a technique to predict bond affinity and conformation between ligands and macromolecules [15]. In this study, molecular docking of HCQ on AGP has been performed. HCQ acts as a ligand, and AGP acts as a macromolecule obtained from the PDB code 3APW. The use of PDB 3APW as a macromolecule is similar to the research previously reported by Nishi et al [16] which also uses the PDP code 3APW as the AGP column representation. The macromolecules was downloaded from the Protein Data Bank (RSCB-PDB) website and then both ligands and macromolecules were prepared by Discovery Studio 2019 software. For simplification, water molecules has been removed from the structure and native ligands is separated from the macromolecules. The grid box is set at 40 x 40 x 40 and the number of modes is maximized to 20. The standard exhaustiveness value of AutoDock Vina is 8, but in this study the value of 246 has been used to increase the accuracy in finding the minimum global point.

In the docking procedure, redocking is the necessary procedure to ensure the validity of the method used. If the complex conformation before and after redocking is similar, then the molecular docking method is considered to be valid. The root-mean-square deviation (RMSD) value was used to measure the similarity [17]. The ideal RMSD will be zero for exactly the same structure, but it is impossible to get a zero value on redocking, so the RMSD value < 2.00 is considered to be valid [18]. The calculation of the RMSD value of redocking has been carried out using the PyMOL software.

To ensure the accuracy of the obtained data, in this study redocking has been carried out in ten repetitions. The RMSD values of 10 redocking are shown in Table 2. The redocking of 8th repetition shows that the interaction between native ligands and amino acids on the active site of AGP has the lowest RMSD value. The level of conformational similarity of native ligands before and after redocking is shown in Fig. 4.

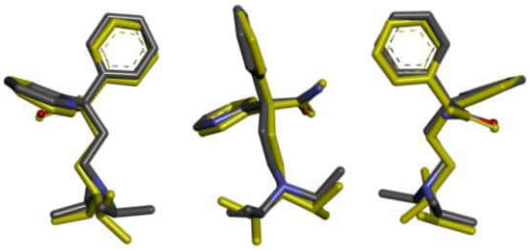


Figure 4. The 3D conformation of native ligand before (yellow) and after (multicolor) redocking with RMSD value of 0.507 (8th redocking)

Table 2. The RMSD values of redocking of native ligand on AGP in 10 repetitions

Redocking	RMSD	Redocking	RMSD
1	1.301	6	1.017
2	1.303	7	1.297
3	1.297	8	0.507
4	1.295	9	1.302
5	1.297	10	1.294

The specific molecular docking parameters for the proposed ligands of R-HCQ and S-HCQ is similar to that of redocking parameters. The specific docking is also done 10 times to ensure its validity and accuracy. Table 3 shows the affinity energy (kcal/mol) values obtained from the molecular docking of the proposed ligands of R- and S-HCQ on AGP using AutoDock Vina.

Table 3. Binding energy of complex HCQ-AGP docked by AutoDock Vina in 10 repetitions

Redocking	Binding energy (kcal/mol)	
	R	S
1	-7.6	-7.2
2	-7.5	-7.2
3	-7.5	-7.2
4	-7.5	-7.2
5	-7.4	-7.1
6	-7.4	-7.1
7	-7.4	-7.1
8	-7.3	-7.1
9	-7.3	-7.0
10	-7.3	-6.9
Average	-7.43	-7.11

In all molecular docking iterations, the R affinity energy is lower than the S affinity energy. The average difference in binding energy between R and S-enantiomers value $|\Delta\Delta G|$ is quite significant, e.g. 0.32 kcal/mol. Therefore, it is predicted that AGP chiral column will be able to separate the HCQ chiral compounds [19]. The more negative binding energy of R indicates that the R-enantiomer interacts more strongly with AGP and therefore it is predicted to be eluted later after S-enantiomer. The visualization of HCQ interaction with AGP using Discovery Studio 2019 are shown in Fig. 5.

In addition to the binding energy, the stability of the interaction of the stereoisomer-AGP complex can also be explained by the presence of hydrogen bonds. Hydrogen bonds between R-HCQ and amino acid residues Try37, Glu92, and Phe112, appear on R-HCQ-AGP complex but are not observed on S-HCQ-AGP resulted from molecular docking. This residue is important in the process of binding AGP to the active site of HCQ. Other types of interaction involving several amino acid residues also appear in the Alkyl/Pi-Alkyl bonds, consisting of Leu79, Val88, Phe51 and Phe112 residues. These types of interaction are observed in the molecular docking of R-HCQ on AGP but does not appear in S-HCQ. The types of interaction between AGP and HCQ chiral compounds docked using AutoDock Vina software are presented in Table 4.

Table 4. Mode of interaction between AGP and HCQ chiral compounds from AutoDock Vina

Enantiomer	Binding energy (kcal/mol)	Mode of interaction			
		Hydrogen bonds	Pi-Pi	Alkyl / Pi-Alkyl	Pi-Sigma
R	-7.6 to -7.3	Try127, Try37, Glu64, Glu92, Ser114, Phe112	Phe112	Ala99, Leu79, Val88, Phe51, Phe112, Phe32, Try37	
S	-7.2 to -6.9	Try127, Glu64, Ser114	Phe112	Ala99, Phe32, Try37	Phe49

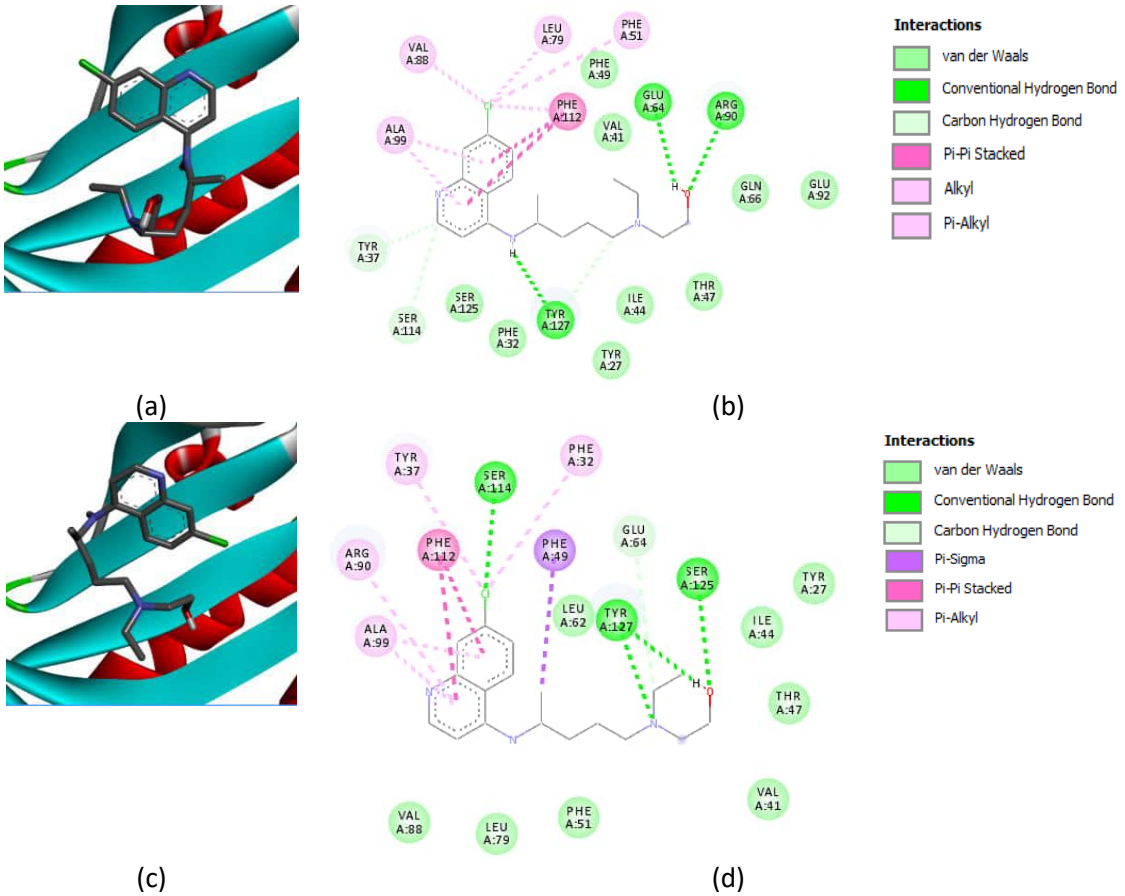


Figure 5. Interaction visualization of (a) 3D R-HCQ (b) 2D R-HCQ (c) 3D S-HCQ and (d) 2D S-HCQ with AGP active sites using AutoDock Vina software

The presence of Pi-Sigma bonds in S-HCQ is an interesting phenomenon. The sigma bond is the strongest covalent bond, but in fact, the total binding energy of S-HCQ is more positive than R-HCQ. This is because the number and mode of interactions in the inclusion complex of R-HCQ with AGP are more diverse rather than S-HCQ with AGP, meaning that there are much more active sites (amino acid residues) involves in the binding of R-HCQ to AGP compared to the binding of R-HCQ to AGP. The difference in the number and types of interaction involved in the inclusion complex gives rise to the difference in binding energy between R-HCQ and S-HCQ which results in the difference in complex stability. Consequently, the two diastereomers of HCQ will be retained differently in the AGP column to yield enantiomer separation.

Summary

The chiral hydroxychloroquine (HCQ) separation on AGP column has been successfully predicted based on the molecular docking approach of HCQ on the chiral α-1-acid glycoprotein (AGP) column. Results of geometry optimization suggest that calculation method based on the DFT/BY3LY with the basis 6-311G gives the best results as compared to experimental ^{1}H-NMR chemical shift data. Molecular docking using AutoDock Vina shows that R-HCQ forms more stable inclusion complex with AGP column, suggesting it will be retained longer in the column and thus S-HCQ will be eluted earlier than R-HCQ. This molecular docking approach is unique and interesting because it can reduce the cost and time in selecting the suitable column and optimizing the separation conditions of HPLC analysis, especially in the chiral separation of drugs.

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