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Molecular Docking Approach for Prediction of Enantioseparation of Chiral Ibuprofen by α-1-Acid Glycoprotein Column

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Abstract. A study of the molecular anchoring and inclusion complex of the R/S-ibuprofen chiral compound with α-1-acid glycoprotein (AGP) has been carried out. This study aimed to predict the chiral separation of ibuprofen using chiral column filled with AGP protein. The geometrical optimization of R/S-ibuprofen was conducted on different calculation methods to obtain the optimal molecular structure. Molecular docking approaches, specifically docking using AutodockTools software were used to predict R/S-ibuprofen separation in AGP chiral column by comparing the binding energy values and the type of interaction. Results of the study show that the best method for optimizing the geometry of ibuprofen is Density Functional Theory (DFT). Furthermore, the results of the specific anchoring of ibuprofen on the AGP show that the binding energy of S-ibuprofen with AGP is more negative than that of R-ibuprofen, namely -5.63 and -5.55 kcal/mol, respectively, indicating that S-ibuprofen interacts more strongly with AGP and therefore it will be eluted from the AGP chiral column later after R-ibuprofen.

Introduction

Ibuprofen is a propionic acid derivative medicine that is a non-steroidal anti-inflammatory drug (NSAID) [1] and used as a painkiller for some diseases such as fever, pain as well as stiffness [2]. In addition, the current studies have mentioned the use of ibuprofen for additional treatment in COVID-19 patients with moderate-severe respiratory symptoms [3]. This medicine is a chiral medicine compound that has two different enantiomers with one chiral center (Fig. 1) where from some reports only one enantiomer gives a good effect while the other form may cause negative effects, therefore, it is important to perform separation. One of the most suitable methods to separate enantiomers of chiral compounds is by using High Performance Liquid Chromatography (HPLC) [4]. However, the separation of chiral medicine with conventional experimentals is not easy and needs a lot of cost.

Nowadays, a popular method for predicting enantiomer separation processes is by utilizing molecular modeling. This modeling is able to cut significantly time and cost consuming in the optimization of separation process by HPLC. The common method used for this purpose is molecular docking between chiral drug and chiral compound of the column [5]. In this study, molecular docking method was conducted to predict the chiral separation of R-Ibuprofen and S-Ibuprofen compounds by chiral column of α-1-acid glycoprotein (AGP). The results of molecular docking was then used to predict which of the enantiomers will be eluted first from the column based on their binding energy values.

Experimental Section

Materials. This study used crystal structure α-1-acid glycoprotein (AGP) with code 3KQ0 which is obtained from Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB). The structure of ibuprofen is treated as a ligand in the docking.

Instrumentation. A personal computer with an Intel Core i3-7100, 3.90 GHz, 8 GB RAM installed with UCSF Chimera 1.14, AutodockTools 1.5.6, Discovery Studio 2020, GaussView 5.0.8, Gaussian® 09W and Notepad^{++} software was used for all studies.

Geometry optimization. The structure of ibuprofen compound was created using GaussView software [6]. The compound was geometrically optimized using Gaussian® 09W [7] by Semi-empirical (SE), Hartree-Fock (HF) and Density Functional Theory (DFT) methods using various basis sets. The optimized compounds were then subjected for ^{1}H-NMR calculations and the results were converted into chemical shifts (δ) and compared to ^{1}H-NMR experimental data reported by Bua *et al.* [8]. Validation of the best method for the calculation was performed by comparing the coefficient of determination (R^2) and PRESS values of δ calculations against the δ values of experimental data.

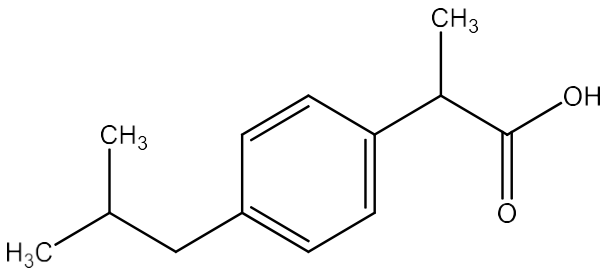


Figure 1. Chemical structure of ibuprofen

Molecular docking. The optimized structure of ibuprofen was used as starting conformation in the molecular docking. α-1-acid glycoprotein (AGP) with 3KQ0 code which is obtained from RCSB PDB was prepared using UCSF Chimera 1.12 [9] before being re-docked. To obtain binding energy, a grid box with the size of 60 Å × 60 Å × 60 Å and the grid resolution of 0.375 Å is used for re-docking by using Autodock Tools 1.5.6 [10]. The Lamarckian Genetic Algorithm (LGA) with parameters set at the default setting was used. Then, the results of 100 re-docking runs were grouped into root mean square deviation (RMSD) group of less than 2.0 Å [11]. From the results of re-docking, 5-10 conformations were selected for docking and the molecular docking results were visualized in Discovery Studio 2020 software [12].

Results and Discussion

Geometry optimization. Geometry optimization is an important part of the basis of computational chemistry. This is because geometry optimization determines the location of atoms so that the most stable molecular conformation is obtained. Stable conformation will produce the lowest energy. This study has used various computing methods, namely SE, HF and DFT. The optimized conformation resulted from each calculation method was subjected for calculation of chemical shifts (δ) of ^{1}H-NMR and the best method was selected by comparing the coefficient of determination (R^2) and the PRESS value of calculated ^{1}H-NMR data against experimental ones. The calculation method was considered to be the best for this ibuprofen compound if the value of R^2 is the closest to 1 and gives the smallest PRESS value. Table 1 shows the value of R^2 and PRESS data of ^{1}H-NMR chemical shifts between experimental and computational results.

Based on Table 1, it can be observed that the highest coefficient of determination (R^2) is given by the HF method and for the lowest PRESS value is obtained from the DFT method. However, the R^2 values of the two methods is not significantly different, while their PRESS values are quite different, showing the DFT method has the lowest one. Therefore, the DFT method with a basis set of 6-31G has been selected as the best method for geometrical optimization of ibuprofen. It has been known that the HF method is commonly used because it has high accuracy, however it requires a long calculation [13]. When it is compared to the DFT method, the DFT method can normally provide the same quality of the results but with simpler computational steps on the same compound [14]. Thus, it is not surprising that in our case the DFT method gives the lowest PRESS values with the R^2 value almost similar to that of SE calculation.

Table 1. Comparison between experimental and calculated ^{1}H-NMR chemical shifts (δ) of ibuprofen obtained by using different calculation methods

Statistical parameters	Calculation methods								
	Semi-empirical (SE)			Hartree-Fock (HF)			Density-functional theory (DFT)		
	PM-6	AM-1	PM-3	3-21G	6-31G	6-311G	3-21G	6-31G	6-311G
R^2	0.9824	0.9673	0.9733	0.9890	0.9962	0.9960	0.9742	**0.9959**	0.9956
PRESS	3.0004	5.7449	4.1023	2.0093	1.6685	2.0590	3.6757	**0.8769**	1.0062

Molecular Docking. Molecular docking is a computational method that describes the interaction of a ligand molecule with a macromolecule. The result of molecular docking is a complex conformation between ligand and macromolecule with the lowest binding energy. Molecular docking can also be applied as a prediction in the separation of chiral compounds. In this way, the separation of chiral compounds can be predicted quickly with a higher degree of accuracy and chiral recognition so that the research costs especially for separation optimization can be reduced. [15].

Table 2. The RMSD values of re-docking calculation

RMSD redocking					
Conf. 1	1.45	Conf. 3	1.86	Conf. 5	2.53
Conf. 2	2.02	Conf. 4	1.28	Conf. 6	1.48

*Conf = conformation

Firstly, the natural ligand and α-1-acid glycoprotein (AGP) that have been prepared are re-docked to yield some ligand conformations that are then justified from their root mean square deviation (RMSD) values. The results of RMSD measurements of some conformations are shown in Table 2. The smallest RMSD value of 1.28 Å is obtained from conformation 4, suggesting that the conformation of natural ligand before and after being re-docked is almost identical. This RMSD value also indicates that the validation criteria of the re-docking method (RMSD < 2.00 Å) is fulfilled.

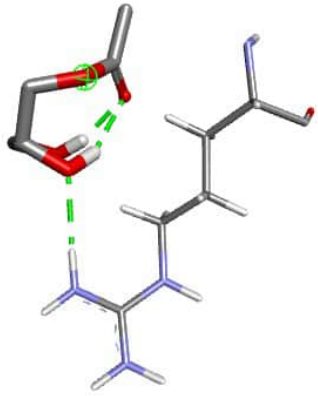
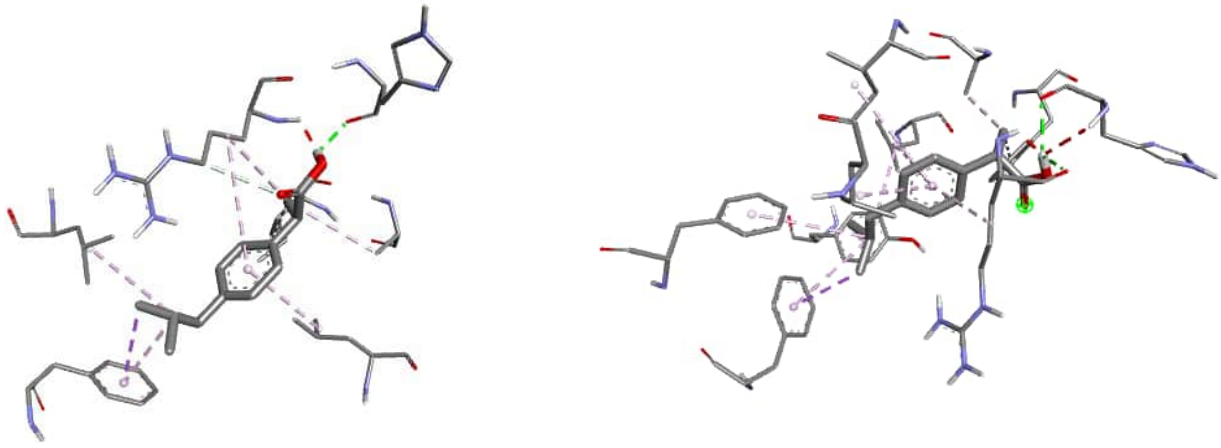


Figure 2. Re-docking bond image of native ligand

Conformation 4 of re-docking result shows the interaction between natural ligand and amino acids on the active side of AGP with the lowest RMSD. The visualization of interaction conformation between ligand and the active side of the AGP is shown in Fig. 2. From this interaction conformation, it can be observed that the hydrogen bonds are formed on the active site of AGP, namely Arg90. These interactions show similarities to the experimental results reported by Schönfeld *et al.* [16], suggesting that our re-docking results are in good agreement with those done experimentally and therefore it can be justified.

In this study, molecular docking of ibuprofen has been performed in a grid box of 60 Å × 60 Å × 60 Å size with 100 runs. The results of molecular docking show the preferred conformation with different binding energies (kcal/mol). It has been obtained from the docking that the estimation of binding energies (ΔG) of R-ibuprofen with AGP is in the range of -5.52 to -5.55 kcal/mol and for S-ibuprofen with AGP is in the range of -5.55 to -5.65 kcal/mol. The negative value of ΔG indicates that the inclusion complexes are stable [5]. While the difference in ΔG between R and S inclusion complex, i.e., |ΔΔG| can be used to describe the enantioseparation distance between R-ibuprofen and S-ibuprofen on AGP columns. The greater value of the |ΔΔG| indicates the better separation of chiral compounds on the used columns. In this study, inclusion complex of S-ibuprofen with AGP has more negative binding energy value (-5.63 kcal/mol) compared to R-ibuprofen (-5.53 kcal/mol), indicating that S-ibuprofen forms more stable inclusion complex than that of R-ibuprofen. Based on the value of |ΔΔG| (0.10 kcal/mol), it can be predicted that the AGP column is able to be used for the separation of the R/S-ibuprofen enantiomer. From the ΔG values, it is clearly understood that the interaction of S-ibuprofen with the AGP column is more stable than R-enantiomer, so that the R-ibuprofen is expected to be eluted first from the AGP column.



(a) R-ibuprofen (b) S-ibuprofen

Figure 3. Visualization images of docking result for (a) R-ibuprofen (b) S-ibuprofen. Hydrogen bond, alkyl/π-alkyl bond, π-σ bond and unfavorable donor-donor bond interactions are shown with green, pink, purple and red color, respectively.

Table 3. Types of interactions between AGP and ibuprofen

Ibuprofen	Binding affinity (kcal/mol)	Interactions			
		Hydrogen bond	Unfavorable donor-donor	Alkyl/π-Alkyl	π-σ
R	-5,53	Arg90	Arg90	Ala99, Leu79, Leu62, Leu112, Phe51	Phe49
S	-5.63	Arg90, His97		Ala99, Ile88, Leu79, Leu112, Phe51, Phe114	Phe49, Tyr127

Aside from the binding energy results, the stability of the stereoisomer complex can be explained by the presence of hydrogen bonds. From Fig. 3, it can be observed that two hydrogen bonds between S-ibuprofen and Arg90 and His97 are formed which are not observed in R-ibuprofen. In addition, the supporting interaction on complex stability is also contributed by the interaction of alkyl/π-alkyl and π-σ, it is well known that the sigma bond is the strongest covalent bond. The differences in R/S-ibuprofen interactions are observed in alkyl/π-alkyl interactions, e.g., Ile88 and Phe114, while for π-σ, interaction with Tyr127 is found only in S-ibuprofen. Details of hydrogen binding, alkyl/π-alkyl and π-σ interactions are summarized in Table 3. The differences in the numbers and types of

interactions between R/S-ibuprofen and the AGP give rise to the stronger bonds of S-ibuprofen to AGP as compared to R-ibuprofen, thus the binding energy of S-ibuprofen is more negative, meaning that the interaction between S-ibuprofen and the AGP column is more stable.

Summary

It has been demonstrated that molecular docking approach can be used to predict the separation of chiral ibuprofen using the chiral column of α-1-acid glycoprotein (AGP). Results of geometrical optimization has suggested that the DFT/BY3LY method with a basis set of 6-31G gives the best results of calculation when it is compared to experimental ^{1}H-NMR data. Molecular docking studies have revealed that S-ibuprofen forms more stable inclusion complex with AGP column than R-ibuprofen. This can be seen from its more negative binding energies as well as the larger numbers and types of interactions which includes hydrogen bond, alkyl/π-alkyl and π-σ interactions. This results predict that R-ibuprofen will be eluted first from the AGP column followed by S-ibuprofen.

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