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Comparative Analysis of the Autodock 4.2 and Autodock Vina Methods in Predicting Thiazolidinedione Interactions with PPARG Receptor

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ABSTRACT

Introduction: *Molecular docking simulation is an in silico method that plays a role in analyzing drug interactions with receptors. The method using Autodock 4.2 and Autodock Vina is widely used for analyzing interactions that occur between ligands and receptors. Aims: This study was aims to compare the Autodock 4.2 and Autodock Vina methods in simulating the docking of thiazolidinedione against PPARG in terms of bond energy and type of interaction parameters.* ***Methods:*** *The method used in this research was molecular docking simulation using Autodock 4.2 and Autodock Vina to compare the interaction results and binding affinity scores in the thiazolidinedione group against PPARG.* ***Result:*** *The results of this study showed that the interactions using the Autodock 4.2 and Autodock Vina methods have some similar amino acids that are bound and the same active site. The binding affinity score showed that the best were troglitazone, pioglitazone, native ligand and rosiglitazone (Autodock 4.2 are -10.66, -9.48, -8.99, and -8.40 kcal/mol respectively; Autodock Vina are -10.5, -9.0, -9.0, and -7.7 kcal/mol respectively).* ***Conclusion:*** *It showed that molecular docking simulations using the Autodock 4.2 and Autodock Vina methods thiazolidinedione with PPARG have similar docking score patterns and almost the same types of interactions.*

KEYWORDS: *Molecular docking, autodock 4.2, autodock vina, thiazolidinedione, PPARG*

INTRODUCTION

Molecular docking is a computational simulation method used to determine interactions between ligands and proteins in the manufacture of medicinal products. This method makes it easier for researchers to discover a drug with the advantages of being fast and economical, but requires expertise in its application. The types of molecular docking methods are rigid and flexible. The interactions that occur in the rigid molecular docking method, the receptor that binds to the ligand, tend to be rigid or their conformation does not change so that the receptor will only bind to the appropriate ligand, while in the flexible method, the interaction between the ligand and the receptor is flexible or its conformation can change shape (Sharma, Kumar, & Narasimhan, 2018; Zloh & Kirton, 2018). This causes the computational

simulation process to occur easily, so this method is used more often than rigid methods. Examples of applications that use flexible molecular docking methods are Autodock 4.2 and Autodock Vina. Autodock Vina is an application development of Autodock 4.2 (Suhandi et al., 2021). The molecular docking method aims to see the interactions that occur between the ligand and the receptor, where in this study the ligand is a thiazolidinedione compound. While the receptor used is Peroxisome Prolifetator Activated Receptor Gamma (PPARG).

Thiazolidinediones are a class of drugs that play a role in lowering blood glucose levels by increasing insulin sensitivity. The mechanism by which thiazolidinediones bind to the active site of the nuclear PPARG, thereby activating PPARG which causes a further signaling process, where there is a decrease in glucose levels in the blood. Some examples of drugs from the thiazolidinediones group include pioglitazone, rosiglitazone, and troglitazone (Irudayaraj et al., 2016; Mazumder et al., 2017).

This research uses two types of docking methods, namely Autodock 4.2 and Autodock Vina. Autodock Vina is an application development from Autodock 4, where Autodock Vina has been designed to be simpler, easier and faster than Autodock 4. Autodock 4 requires an autogrid stage in the docking process, while Autodock Vina is programmed automatically. However, Autodock 4 can produce more complex ligands than Autodock Vina. The parameters that influence the docking process include hydrogen bonds, van der Waals bonds, electrostatic energy and desolvation free energy (Nickavar, 2022; Sandeep, Nagasree, Hanisha, & Kumar, 2011). So this research aims to compare the Autodock 4.2 and Autodock Vina methods in the interaction of thiazolidinedione compounds with PPARG in terms of the binding affinity energy parameters and the type of bond that occurs. This research is important to determine the differences in results between the 2 types of molecular docking methods. So the results of this research can later be used as a consideration in choosing a molecular method for docking compounds against the PPARG receptor.

MATERIAL AND METHODS

Software, hardware, ligand and protein preparation

This research used a set of computer tools which have specified Asus X455L Intel Core i3-insideTM. Software which in that were installed Autodock Tools, Discovery Studio 2021, Autodock 4.2 and Autodock Vina version 1.1.2. The three-dimensional (3D) chemical structure in this study consists of the ligand Pioglitazone (Pubchem CID: 4829), Rosiglitazone (Pubchem CID: 77999), and Troglitazone (Pubchem CID: 5591) were obtained through the website http://pubchem.ncbi.nlm.nih.gov/, while the 3D structure of Activated Peroxisome Proliferator Receptor Gamma (PPARG, pdb

id: 6dha) was downloaded from the website https://www.rcsb.org/..

The initial step of this research is to download the 3D structure of the drug compound pioglitazone, rosiglitazone, and troglitazone obtained through the website http://pubchem.ncbi.nlm.nih.gov/, then prepared in the initial stage using the application Autodock Tools. This preparation aims to determine the number of atoms that rotate appropriately the amount of torque on each molecule, where the preparation results are stored in a format pdbqt. Meanwhile, the 3D PPARG structure, pdb id: 6dha is downloaded via the website https://www.rcsb.org/, which is then prepared at an early stage using apikasi Discovery Studio 2021. This preparation aims to remove ligands and water components bound, where the preparation results are saved in pdb format. Next, more preparation This is further carried out on the receptor to change its format to pdbqt using Autodock Tools. The results of the preparation of ligands and receptors have been obtained in this format the same (pdbqt), then a molecular docking process is carried out for each compound docked using 2 methods, namely Autodock 4.2 and Autodock Vina (Garrett M. Morris, 2010; Nickavar, 2022). The ligands resulting from the docking process are analyzed for the type of interaction between them ligands and receptors using the Discovery Studio 2021 application. Results of both method processes the dockings obtained are then compared.

Molecular docking simulation using autodock 4.2 and autodock vina methods

PPARG in pdbqt format was prepared using Autodock Tools which determines the simulation grid area (docking active site based on the coordinate position of the original ligand). The initial stage is re-docking, which was done again to determine whether the docking simulation parameters can be used for other compounds or not. The coordinate grid area simulation used in this research was with coordinate position x = 18,856; y = 64,889; and z = 14.322.

This research was using Autodock 4.2, the box size parameters used in this research are 40x40x40 with grid spacing of 0.375 Angstrom. The docking parameters used were the Lamarcking Genetic Algorithm and other parameters are made default. Meanwhile, in the Autodock Vina method, the box size used in this research is 18x18x18 with a grid spacing of 1 Angstrom. The docking parameters used were the Gradient Optimization Algorithm and other parameters were made default. If the re-docking result is below 2 Angstroms, the docking parameters that have been selected can be used for the compounds pioglitazone, rosiglitazone, and troglitazone (Arunkumar et al., 2022; Lateef, Naeem, & Qureshi, 2020; Shivanika et al., 2022). The output of the docking simulation using the Autodock 4.2 method was the binding affinity score and the binding interactions between the ligand and the

receptor which was analyzed using Discovery Studio 2021 software.

RESULTS AND DISCUSSION

The initial stage of the molecular docking method is re-docking, where the parameter looked at is the Root mean square deviation (RMSD). As for the provisions indicating that the parameters in carrying out docking simulations can be used for other test compounds, generally the RMSD value of the re-docking results is < 2 Å (Miñarro-Lleonar, Ruiz-Carmona, Alvarez-Garcia, Schmidtke, & Barril, 2022; Rashid et al., 2022; Suhandi et al., 2021). Based on the results of molecular docking simulations using both the Autodock 4.2 and Autodock Vina methods, it shows that the RMSD values are 1.91 Å and 1.9 Å respectively. This means that the parameters used for the Autodock 4.2 and Autodock Vina methods can be used to test molecular docking simulations of other compounds to PPARG receptor.

One of the differences between the docking scores in the Autodock 4.2 method and Autodock Vina is due to the difference in the algorithm used. The binding affinity energy calculation algorithm in the Autodock 4.2 method is the Lamarckian Genetic Algorithm and the free energy assessment function is empirical. Meanwhile, the binding affinity energy calculation algorithm in the Autodock Vina method is the Gradient Optimization Algorithm which was designed and implemented by Dr. Oleg Trott in the Molecular Graphics Lab at The Scripps Research Institute. Various types of algorithms used in molecular docking may influence the conformation of molecules resulting from molecular docking simulations. However, even though the algorithms used are different, it is possible that the docking results can be similar or different, depending on the conformation of the docking simulation results for each method (Nickavar, 2022; Shivanika et al., 2022; Suhandi et al., 2021). Based on the docking score results in the form of binding affinity energy, the best for the Autodock 4.2 and Autodock Vina methods are troglitazone, pioglitazone, native ligand and rosiglitazone, respectively. So the binding affinity energy results in the Autodock 4.2 and Autodock Vina methods have the same compound sequence (Table 1). Table 1. Binding Affinity Energy from thiazolidindione to PPARG using Autodock 4.2 and Autodock Vina Methods.

The docking simulation result of native ligand using the autodock 4.2 method, it was found that the oxygen atom in the native ligand bonds with the hydrogen atom in amino acid His 323 and Ser 289 to form a hydrogen bond, and the hydrogen atom in the native ligand bonds with the oxygen atom in amino acid

Table 1. Binding affinity energy from thiazolidindione to PPARG using Autodock 4.2 and Autodock Vina Methods

Molecule	Binding Affinity Energy (kcal/mol)	
	Autodock 4.2	Autodock Vina
Native Ligand	-8.99	-9.0
Pioglitazone	-9.48	-9.0
Rosiglitazone	-8.40	-7.7
Troglitazone	-10.66	-10.5

Ser3 42. Apart from that , the pyridine group of the native ligand interacts with amino acid Ile 341 to form a Pi-Sigma bond. Next, the aromatic ring on the native ligand interacts with the alkyl group on amino acid Cys 285, Arg 288, and Leu 330 to form a Pi-Alkyl bond. There is an interaction van der Waals between amino acids from the hydrophobic group on the native ligand on amino acid Leu 340, Leu 453, Leu 465, Leu 469, Val 339, Ile 326, Phe 282, Phe 363, His 449, Gln 286, Tyr 327, Tyr 473, and Met 364 (Figure 1). The docking simulation result of native ligand using the Autodock Vina method, it was found that the oxygen atom in the native ligand bonds with the hydrogen atom in amino acid Tyr 473, Cys 285, and Ser 342, thereby forming a hydrogen bond. The oxygen atom in the native ligand interacts in an Unfavorable Donor-Donor manner with amino acid Ser 289. The aromatic ring of the native ligand interacts with the alkyl group on amino acid His 449 to form a Pi-Cation interaction. The Pi-Alkyl interaction occurs on the aromatic ring of the native ligand which interacts with the alkyl group on amino acid Leu 330 and Arg 288, and the alkyl group on the native ligand interacts with the hydrogen atom on amino acid Leu 453, Leu 465, and Leu 469. In The results of this method also contain van der Waals interactions from the hydrophobic group on the native ligand with amino acid Gln 286, His 323, Phe 282, Phe 363, Lys 367, Tyr 327, Met 334, Met 364, Val 339, Gly 284, Leu 340, Ile 281, and Ile 341. In the Autodock 4.2 method there are 4 amino acids that are not obtained in this method, namely amino acid Lys 367, Met 334, Gly 284, and Ile 281 (Figure 1). Meanwhile in the Autodock Vina method there is 1 amino acid that is not obtained in this method, namely amino acid Ile 326. Apart from the amino acid, other amino acids are the same as those obtained from each method.

The docking simulation result of pioglitazone results obtained from the autodock 4.2 method are that there is a hydrogen bond interaction that occurs at the oxygen atom of pioglitazone which interacts with the hydrogen atom of amino acid His 323 and Ser 289. The Pi-Cation interaction occurs in the aromatic group which bonds with the alkyl group on amino acid Met 362. The aromatic group in pioglitazone also interacts with the alkyl group in amino acid Tyr 327 which forms a Stacked Pi-Pi bond. The pyridine group in pioglitazone binds to amino acid Ile 341 to form a Pi-Sigma bond. In the same pyridine group, there is a Pi-Alkyl interaction with the alkyl group on amino acid Met 348 and Val 339. The alkyl group on pioglitazone interacts with the hydrogen atom on amino acid Ile 281 and Met 348. Regarding van der Waals interactions, including Leu 330, Leu 353, Leu 453, Leu 465, Leu 469, Ile 326, Phe 282, Phe 363, Tyr 473, His 449, Gln 286, Lys 367, and Gly 284. In this docking result, Pi-Donor Hydrogen Bond interactions also occur. In the docking results of pioglitazone using the Autodock Vina method, hydrogen bonding interactions occur on the oxygen atom

of pioglitazone which bonds with the hydrogen atom of amino acid Ser 342 and Cys 285. Pi-Cation interactions occur in the pyridine group of pioglitazone which bonds with the alkyl group on amino acid His 449. The aromatic group of pioglitazone binds to the alkyl group on amino acid LEU 330 and ARG 288, and the alkyl group of pioglitazone interacts with the hydrogen atom on amino acid Leu 453, Leu 465, Tyr 473, and Phe 282. Van der Waals interactions occur on the hydrophobic group on pioglitazone against amino acid of Val 339, Ile 281, Ile 326, Ile 341, Met 364, Lys 367, Tyr 327, Gln 286, Leu 469, His 323, and Gly 284. The Pi-Donor Hydrogen Bond interaction on the pyridine group of pioglitazone which binds to amino acid Ser 289. The docking results obtained from the Autodock 4.2 method show the absence of amino acid Ser 342 and Arg 288 as the two amino acid obtained from the Autodock Vina method (Figure 1). Meanwhile, the docking results obtained from the Autodock Vina method showed the absence of amino acid Leu 353, Phe 363, and Met 348 as obtained from the Autodock 4.2 method. The other amino acids were each obtained by both methods.

The docking results obtained using the Autodock 4.2 method show that the Pi-Cation bond occurs on the S atom of rosiglitazone with the alkyl group on amino acid His 323 and Tyr 473, as well as on the pyridine group bonding with the alkyl group on amino acid Arg 288. In the same pyridine group, this occurs. Pi-Sigma bond interaction with the alkyl group on amino acid Ile 326. In the same pyridine group there is also a Pi-alkyl bond which interacts with the alkyl group on amino acid Leu 330 and Ala 292, while the same interaction occurs with the rosiglitazone aromatic group which bonds with the alkyl on amino acid Cys 285. The van der Waals interaction of the hydrophobic group on rosiglitazone on amino acid Met 329, Met 364, Leu 333, Leu 452, Leu 465, Leu 469, Tyr 327, His 449, Gln 286, Phe 282, Phe 363 , Lys 367, and Ser 289. The docking results obtained using the Autodock Vina method show that there is a Pi-Cation bond in the pyridine group of rosiglitazone which is bound to the alkyl group on amino acid His 449. In the same pyridine group there is a Pi-Donor Hydrogen Bond interaction which is bonded to the hydrogen atom on amino acid Ser 289 , while in the aromatic group of rosiglitazone there is a Pi-Donor Hydrogen Bond interaction which bonds with the hydrogen atom on amino acid Cys 285. In the same aromatic group there is a Pi-Alkyl bond which bonds with the alkyl groups of Leu 330 and Arg 288. The van der Waals interaction of hydrophobic group on rosiglitazone against amino acid Gly 284. Met 348, Met 364, Ile 281, Ile 326, Ile 341, Phe 363, Lys 367, Gln 286, Tyr 327, Tyr 473, Leu 469, His 323, and Val 339. The docking results obtained from the Autodock 4.2 method show the absence of amino acid Gly 284, Met 348, Ile 281, Ile 341, and Val 339 as the amino acid obtained from the Autodock Vina method (Figure 1).

Meanwhile, the docking results obtained from the Autodock Vina method showed the

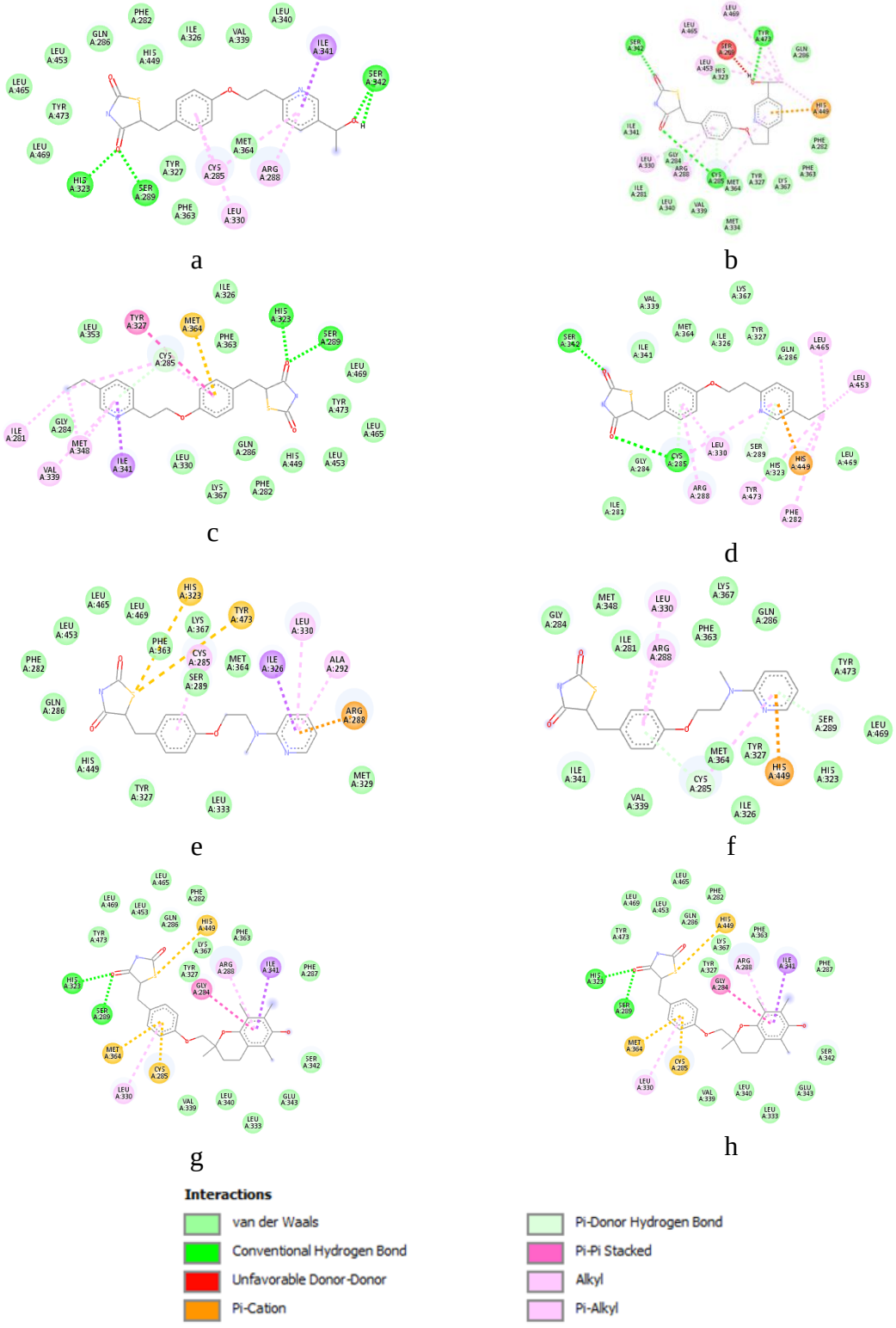


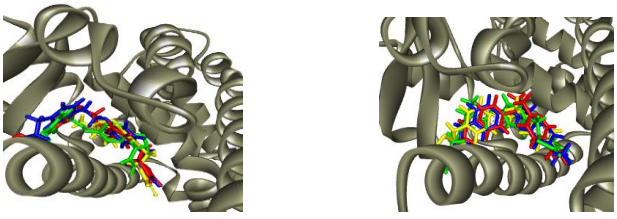
Figure 1. Binding interaction two dimension between thiazolidindione to PPARG using Autodock 4.2 and Autodock Vina methods. a. Native ligand (Autodock 4.2 methods) b. Native ligand (Autodock vina methods) c. Pioglitazone (Autodock 4.2 methods) d. Pioglitazone (Autodock vina methods) e. Rosiglitazone (Autodock 4.2 methods) f. Rosiglitazone (Autodock vina methods) g. Troglitazone (Autodock 4.2 methods) h. Troglitazone (Autodock vina methods)

absence of amino acid Met 329, Leu 333, Leu 453, Leu 465, Phe 282, His 323, and Ala 292 as obtained from the Autodock 4.2 method. The other amino acids were each obtained by both methods.

The docking simulation result of troglitazone using the Autodock 4.2 method show that there is a Pi-Cation interaction between the S atom in troglitazone which is bound to the alkyl group on amino acid His 323. The same interaction also occurs in the aromatic group of troglitazone which is bound to the alkyl group on amino acid Met 364. In The same aromatic group occurs as a Pi-Alkyl interaction which bonds with the alkyl group on amino acid Arg 288 and Leu 330. In the tetrahydropyran group troglitazone bonds with the alkyl group on amino acid ARG 288, and in the alkyl group troglitazone interacts with the hydrogen atom on amino acid Leu 330, Leu 333, Leu 353, Val 339, and Met 348 form Pi-Alkyl bonds. The Pi-Sigma interaction occurs between the aromatic group of troglitazone and the alkyl group on amino acid Ile 341. The hydrogen atom of troglitazone interacts with the oxygen atom on amino acid Ile 281 to form a hydrogen bond. The Pi-Donor Hydrogen Bond interaction occurs in the aromatic group which bonds with the alkyl group on amino acid Cys 285 and on the oxygen atom which bonds with the alkyl group Gln 286. Van der Waals interactions occur from the hydrophobic troglitazone group on amino acid Gly 284, Ser 289, Ser 342, Lys 367, Ile 326, Tyr 327, Tyr 473, His 449, Leu 340, Leu 469, Phe 282, and Phe 363. The docking simulation result of troglitazone using the Autodock Vina method show that hydrogen bonds occur at the oxygen atom of troglitazone which interacts with the hydrogen atom on amino acid His 323 and Ser 289. The sulfur atom of troglitazone interacts with the alkyl group on amino acid His 449, and the aromatic group interacts with The alkyl groups on amino acid Met 364 and Cys 285 form Pi-Cation bonds. In other aromatic groups in troglitazone there is a Pi-Pi Stacked interaction which bonds with the alkyl group on amino acid Gly 284. In the same aromatic group there is a Pi-Sigma bond which interacts with the alkyl group on amino acid Ile 341. The Pi-Alkyl bond occurs between the aromatic groups with the alkyl group on amino acid Leu 330 and Arg 288. Van der Waals interactions occur from the hydrophobic group of troglitazone to amino acid of Tyr 327, Tyr 473, Leu 330, Leu 340, Leu 453, Leu 465, Leu 469, Gln 268, Glu 343, Phe 282, Phe 287, Phe 363, Lys 367, Ser 342, and Val 339. The docking results obtained from the Autodock 4.2 method show the absence of amino acid Ile 281, Ile 326, Met 348, and Leu 353 as the amino acid obtained from the Autodock Vina method Based on 3-dimensional interactions using both the Autodock 4.2 and Autodock Vina methods, it shows that all compounds in the thiazolidinedione group occupy the active site of the receptor like native ligand compounds (Figure 1). Meanwhile, the docking results obtained from the Vina autodock method showed the absence of

amino acid Glu 343 and Phe 287 as the two amino acids obtained from the Autodock 4.2 method. The other amino acids were each obtained by both methods. Based on 3-dimensional interactions using both the method .

Autodock 4.2 and Autodock Vina methods, it shows that all compounds in the thiazolidinedione group occupy the active site of the receptor like native ligand compounds (Figure 2). Based on the molecular docking results, it shows that the two methods have similar binding affinity energy patterns but there are several differences in the types of interactions with the receptor targets. This could be because the two docking methods produce different conformational forms of the compound, so that some of the bonds that occur are the same and some are different. The binding affinity energy is similar even though the conformation forms and types of interactions are different because the total binding affinity energy is the total of all types



a b

Figure 2. Interaction three dimension between thiazolidindione to PPARG using Autodock 4.2 and Autodock Vina methods (Note: Native Ligand: Red; Pioglitazone : Blue; Rosiglitazone : Yellow; Troglitazone : Green a. Autodock 4.2 methods b. Autodock vina methods.

of bond energy that occur between the compound to PPARG receptor.

CONCLUSION

Based on the re-docking results of the Autodock 4.2 and Autodock Vina methods, it shows that both methods can be used for molecular docking simulations of thiazolidinedione compounds against the PPARG receptor. Meanwhile based on from the binding affinity energy parameters of compounds in the thiazolidinedione group towards the PPARG receptor, show that both the Autodock 4.2 and Autodock Vina methods are in the same order, the best respectively being troglitazone, pioglitazone, native ligand and rosiglitazone. Meanwhile, the bond interaction parameters that occur between thiazolidinedione compounds and the PPARG receptor show that the type of interaction and the amino acids bound by the ligand are not much different. So it can be concluded that the Autodock 4.2 and Autodock Vina methods show similar molecular docking simulation results between thiazolidinedione compounds against the PPARG receptor.

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