International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 12, Issue 4, 2020

Original Article

MOLECULAR DOCKING STUDIES OF HGV-6 ANALOGUE AS A POTENTIAL PBP-1A INHIBITOR

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Received: 17 Dec 2019, Revised and Accepted: 14 Feb 2020

ABSTRACT

Objective: The sygnificance of this study is to find a new hexagamavunon-6 analogue (HGV-6); 3,5-bis-(4′-chlorobenzylidene)-tetrahydro-4H-thiopyran-4-one (D144); 3,5-bis-(2′,4′-dichlorobenzylidene)-tetrahydro-4H-thiopyran-4-one (D154); 3,5-bis-(3′,5′-dichlor ro-4′-hydroxybenzylidene)-tetrahydro-4H-thiopyran-4-one (D156) as a potential PBP-1A inhibitor.

Methods: Docking method through Molecular Operating Environment (MOE) software was used to design a new HGV-6 analogue and study its interaction with penicillin binding protein (PBP-1a). This docking study used parameterized model 3 (PM3) method through Polak Ribiere algorithm to calculate the optimal structural geometry of the compound. Protein validation was carried out to ensure that the protein was suitable for use.

Results: The results of the docking study show that the docking scores of D144 (-9.7942) and D154 (-10.1961) are higher than D156 (-12.2604), while D156 is lower than HGV-6 (-11.7958). Ampicillin (-13.6496) as a native ligand has the smallest docking score compared to the test compounds.

Conclusion: The results of the docking study show that 3,5-bis-(3,5-dichloro-4-hydroxybenzylidene)-tetrahydro-4H-thiopyran-4-one (D156) has a better potential antibacterial compound than HGV-6.

Keywords: Molecular docking studies, Chemical interaction, 3,5-bis-(3,5-dichloro-4-hydroxyzylidene)-tetrahydro-4H-thiopyran-4-one (D156), antibacterial

DOI: http://dx.doi.org/10.22159/ijpps.2020v12i4.36648. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps

INTRODUCTION

The development of research on the new antibacterial drug for treating life-threatening infectious diseases is urgent. The development of antimicrobial resistance has increased during this century, so the development of new antimicrobial agents that are more selective, stronger and lower toxic than the drugs that have been used clinically is urgently needed. Curcumin, (*E*,*E*)-l,7-bis-(4-hydroxy-3-methoxyphenyl)-l,6-heptadiene-3,5-dione, also known as turmeric, is a natural yellow pigment derived from the root of *C. tinctoria, C. xanthorrhiza* and *C. domestica* has been used for centuries. It is used as a food coloring agent and for traditional medication in India [1] to treat various diseases including billary disorder, anorexia, cough, diabetic wounds [2], many types of cancer, antiinflammatory [3], antispasmodics, antimicrobial [4], antimicrobiota for digestive tract.

Monocarbonyl analogue of curcumin (MAC) no 74-94 by curcumin 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiena-3,5-dion has gained a lot of attention from researchers [5]. The effect of curcumin structural modification can increase stability and solubility, which involve the elimination of keto-enol forms which are prone to hydrolysis, including various alternative substituents on the terminal phenyl ring [6]. In the design of modern drug, molecular docking is regularly used to find out drug receptor interactions. Molecular docking provides useful information about the drug receptor interactions and is often used to predict the orientation of the candidate bonds of small molecule drugs with target protein to predict molecular affinity and activity [7].

Istyastono [8] had carried out molecular analogue of curcumin to obtain lead compounds in the development of dipeptidyl peptidase-4 inhibitor. Yuniarti [9] had also conducted *in vitro* and *in silico* studies on curcumin and its analogues as dual inhibitors of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) fig. 1.

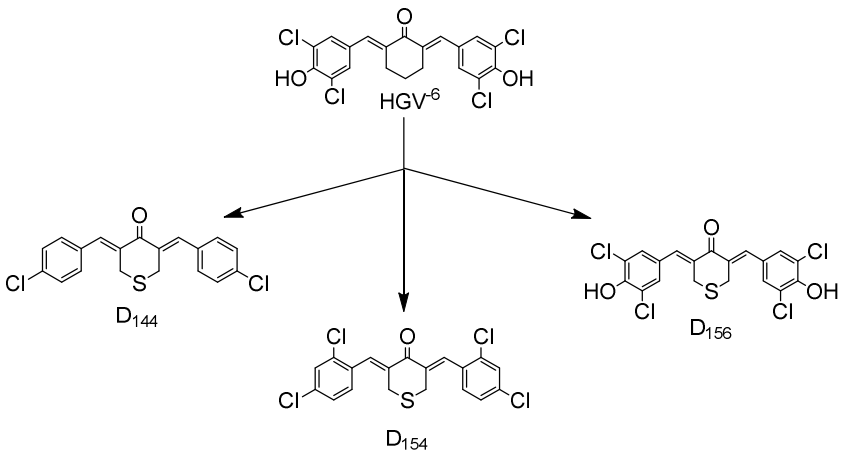

Fig. 1: Modification of HGV-6

New analogues of HGV-6 compounds with the codes D144, D154 and D156 with the main chain S-heterocyclic, substituents of chlorine (-Cl), hydroxy (-OH) in the side chain and imidazole analogue [10] suspected to have activities such as HGV-6. Screening of the three compounds is used as a basis for the presence or absence of changes in the substitutes for their antibacterial activity.

Penicillin binding proteins (PBPs) are enzymes for the polymerization of the glycan strands and the cross-linking between glycan chain and the target protein for β-lactam antibiotics. Mutational changes in PBP can cause resistance either by reducing the antibiotic binding to the active site or by increasing the activity of β-lactamase degrading antibiotics [11]. Penicillin and cephalosporin are two compounds of β-lactam group with the main structure of N-heterocyclic carbonyl in which it activates PBPs in the formation of bacterial cell walls. Given that, the analogues of curcumin with the main structure resembling β-lactam is suspected to have antibacterial potential. Twelve PBPs have been characterized in *E. coli* [1]. These proteins are divided into two groups that are high and low molecular weight (MW). High molecular weight PBP1a, PBP1b, PBP2 and PBP3 are bifunctional enzymes with DD-transpeptidase and transglycosidase activities. Seven PBPs with low BM are found in *E. coli*, but not essential. *E. coli* is missing gene in all PBPs with low molecular weight, but it still lives in the medium with PBP2 and PBP3, at least either PBP1a or PBP1b becomes very important since they have transpeptidase activities to synthesize the peptidoglycan [1]. Based on the test, the target protein is PBP-1a with code 5hl9. By using of such target protein, it is expected that the results of the *docking* can explain the potential of analogues of HGV-6 compounds D144, D154 and D156.

The results of the research above have led us to carry out molecular docking test for the four compounds with the main structure S-heterocyclic. To find out the ligand-protein interaction, the interaction part of the compounds is clearly described. It is the basis for studying the interaction of ligands with receptor proteins of bacterial cell walls.

MATERIALS AND METHODS

Materials

3,5-bis-(4′-chlorobenzylidene)-tetrahydro-4H-thiopyran-4-one (D144); 3,5-bis-(2′,4′-dich lorobenzylidene)-tetrahydro-4H-thiopyran-4-one (D154); 3,5-bis-(3′,5′-dichloro-4′-hydro xybenzylidene)-tetrahydro-4H-thiopyran-4-one (D156); 2,6-bis-(3′,5′-dichloro-4′-hydroxybenzylidene)-cylcohexanone (HGV-6), PBP 1a).

Instrumentation

The molecular docking was using a Personal computer with Intel core i3-6006U 2.0 GHz, ram 4GB, window 7 operating system. The Molecular docking procedure was performed using the Molecular Operating System (MOE) software version 2015.01.01.

Procedure

Ligand structure preparation

The four compounds and ampicillin as reference molecules from molecular docking simulation were built with a two dimensional model and formed with MOE software. The conformation determination was using MOE software by import conformation, then the minimum energy was calculated.

Protein validation (5HL9)

The protein crystals had a crystal resolution of 2.7 Å with 78% of the protein chain having a high fit residue to electron density and no outlier. Native ligand alignment and dock ligand alignment were performed to ensure that the 5HL9 protein was suitable for use.

Docking simulation

3D Penicillin Binding Protein (PBP-1a) was obtained from Protein Data Bank (https://www. rcsb. org/structure/5hl9; code ID, PDB: 5hl9) [12]. The protein contains reference molecule which was ampicillin as native ligand. The protein binding site was regulated using an atom ligand selection module in MOE and ampicillin binding site was used in the crystal structure as a reference. The binding site sequence was set using the MOE program. Hydrogen was added to complete the protein structure using the Protonate 3D program on MOE, only the ligand and protein chain were selected from the crystal structure. The protein was then aligned using the Align MOE module. In the docking simulation process, placement was set on the triangular matcher, rescoring was set with the London dG parameter and the conformation number was set at 10 poses. The selected conformation with rmsd value<2Å was used for molecular docking [13]. The results of the docking of output file in the form of mdb with some conformation were compared to the results of docking of native ligand and positive control of ampicillin. All docking conformations were analyzed and the best value in the right pose was chosen for further interaction studies [14].

RESULTS AND DISCUSSION

The research on D144, D154 and D156 was evaluated *in silico* as antibacterial. Molecular docking of the four compounds to β-lactam receptor was performed according to the basic components of the formation of D-Alanil-D-Alanine at the peptidoglycan formation stage. Transport enzyme D-Alanil-D-Alanine was D-Alanil-D-Alanine decarboxylase (DACA). Protein with code ID, PDB: 5HL9 was provided by the protein data bank. The protein containing reference molecule was ampicillin as the native ligand [15]. Validation of molecular docking protocols was conducted to ensure that the receptors were suitable for use in the molecular docking process. Based on the protein validation process, it obtained a root mean square deviation (RMSD) of 1.5042 Å where its value was less than 2Å indicating that the docking method with 5HL9 receptor was valid and suitable for the further docking process [9] fig. 2.

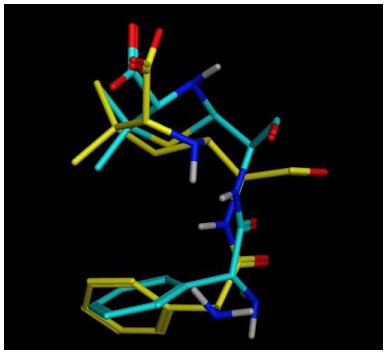

Fig. 2: Alignment native ligand (cyan) and docked ligand (yellow) PDB ID: 5HL9

The best suit of maximum number of interactions had been analyzed, indicated by the S value in the MOE software. The best docking pose of 10 conformations of each compound analyzed for interaction research. Docking results indicating the lowest binding energy cluster were considered as representative binding states. The minimum binding energies showed that target proteins were docked successfully with ligand molecules as an antibacterial agent [16]. Docking result revealed the strongest interaction had the right pose. Protein ligand interactions were visualized in 2D and 3D using MOE table 1.

Tabel 1: Docking results with protein PDB ID 5HL9

Compound	S	E_conf	E_place	E_score1	E_refine	No. of Conf
D144	-9.794	16.071	-58.138	-9.488	-26.494	10
D154	-10.196	21.145	-55.990	-10.049	-20.787	10
D156	-12.260	20.316	-62.222	-11.129	-23.352	10
HGV-6	-11.795	43.583	-82.049	-12.013	-28.683	10
Ampicilin	-13.649	-47.261	-57.702	-9.794	-46.015	10

The results of D144, D154 and D156 docking using IDB ID receptor: 5HL9 with HGV-6 and ampicillin as a reference show the docking scores of-9,7942,-10,1961,-12,2604. From the three ligands, it was seen that D156 had the lowest docking score, meaning that D156 had the best antibacterial potential to interact with the target protein. In general, the difference in the electronegative group substituents in a compound affected the potential of the compound.

Native ligand of ampicillin showed important amino acids that interacted with target proteins such as Asn574, Thr701, Ser510, Lys698. In its interactions, ampicillin involved O (C = O) atom from the carbonyl amide group interacting with Asn574 residues via hydrogen bonds (H-acceptor), carbonyl O (C = O) in carboxylic group interacting with Thr701 via hydrogen bonds (H-acceptor) and the carboxylate group of O (OH) with Ser510 and Lys698 interacting via ionic bonds fig. 3.

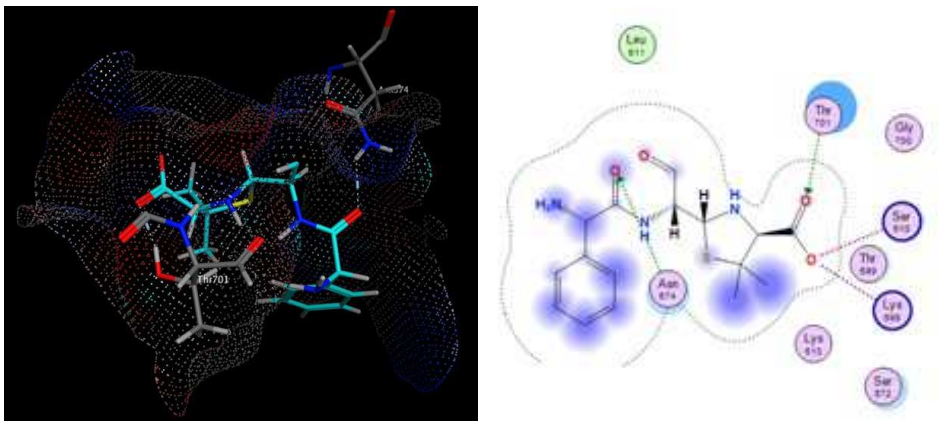

Fig. 3: Binding surface and ligand interaction of ampicillin with 5HL9

D144 interacted with amino acid Asn574, involving the interaction of phi coordination bonds in the benzene ligand group with H atoms on Asn574. This interaction had similarities with native ligand namely involving Asn574, so the compound had potential as an antibacterial fig. 4.

Compound D154 with two Cl substitute had no antibacterial activity against the target protein, even though the docking score showed greater than compound D144 who having one Cl substituent fig. 5.

That was because the geometry of Cl atom formed tetrahedral sp3 in ortho position would disturb the other atoms around it (steric factors) so that it could inhibit resonance into the aromatic ring. The steric effect of the Cl atom in ortho position caused the compound ability to resonate towards the Cl substituent in para position, so the compound's electrophilicity decreased so there was no interaction with the target protein. D156 showed similar interaction with native ligand since the structure of test compound had an interaction involving the amino acid Ser510 via H donor and Asn574, H acceptor via hydrogen and semipolar bonds. Theoretically, chlorine atom would deactivate the benzene ring, but *in silico* illustrated that electronegative atom was the center of action other than carbonyl since it seemed that some amino acids could interact with it fig. 6.

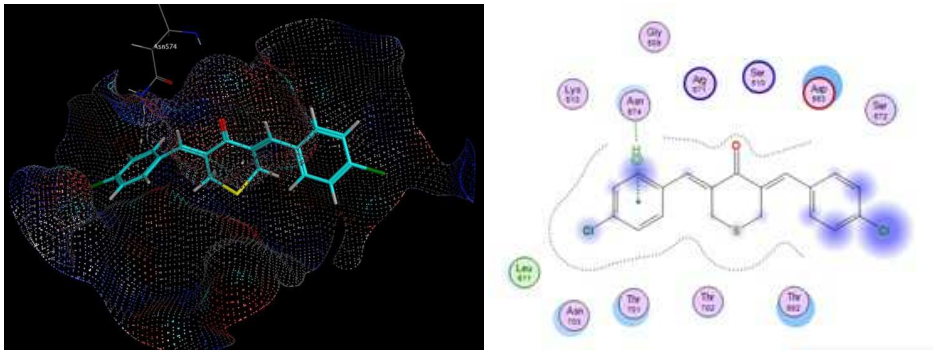

Fig. 4: Binding surface and ligand interaction of D144 with 5HL9

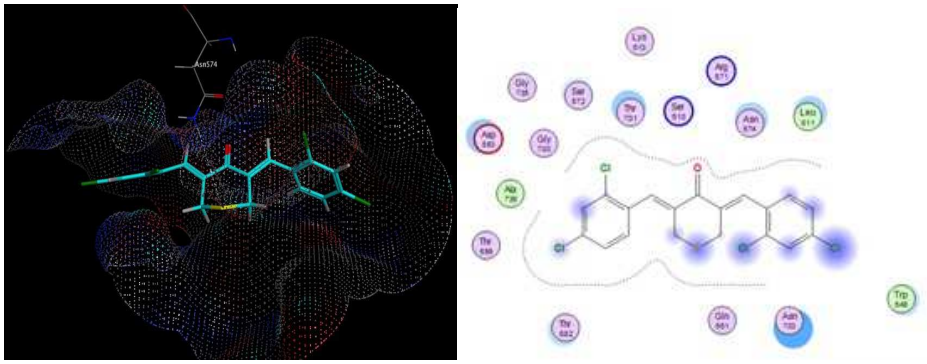

Fig. 5: Binding surface and ligand interaction of D154 with 5HL9

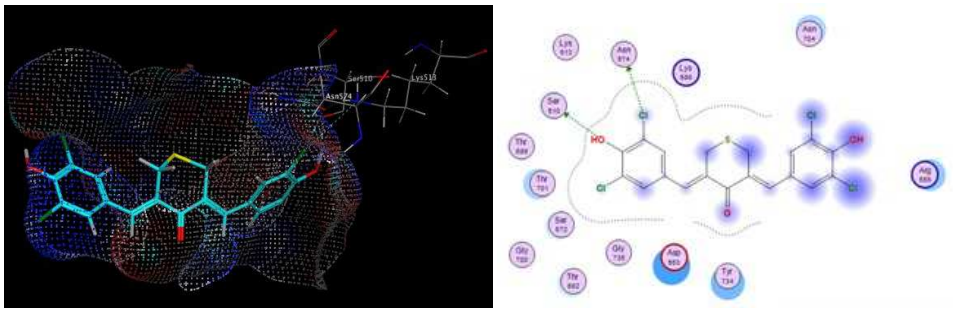

Fig. 6: Binding surface and ligand interaction of D156 with 5HL9

D156 had the greatest potential as an antibacterial than the other three D and HGV-6 compounds since it had the lowest s value and the most interacting with active residue. This means that D156 is most active as antibacterial than other D compound and HGV-6. This compound had two different substituent groups which were Cl and OH, where these groups are pharmacophores acting as binding sites of the target protein. A lower docking score with the right pose resulted in a better stability level of ligand and receptor [17]. The lower binding energy indicated, the more likely it was to accept this test compound as a drug [16].

HGV-6 showed interactions in the Cl atom interacting with Ser507 via H-donor fig. 7. From the docking score, it was more potent than D144 and D154 but since the involved amino acid was not the same as native ligand, the compound had lower antibacterial properties than D156 fig. 7.

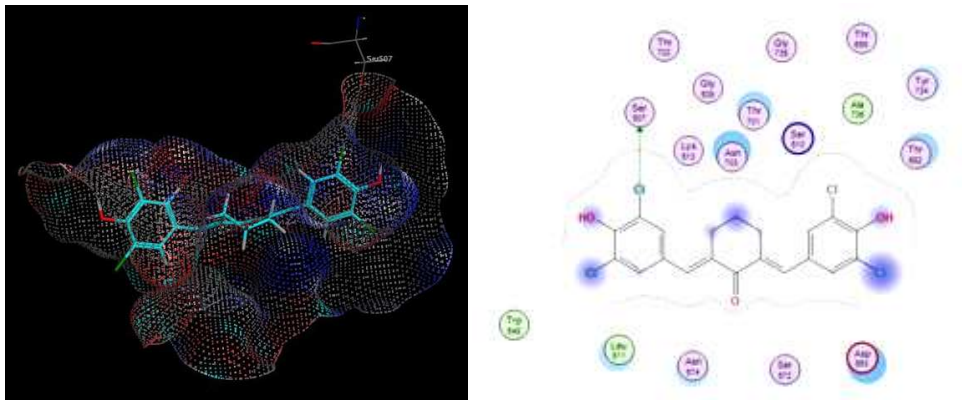

Fig. 7: Binding surface and ligand interaction of HGV-6 with 5HL9

CONCLUSION

The research on the interaction of chemical ligands with proteins could be explained using the MOE docking program. Each compound had a different active site depends on the substituents, heteroatom groups, and molecular geometries. Hydrogen bonds were formed through the electrostatic interactions of electron pairs from the O carbonyl atom to amino group, semipolar bonds were formed due to the contribution of a free electron pair to another atom. D156 was stronger than other D and HGV-6 compounds through hydrogen and semipolar bonds to a protein target.

ACKNOWLEDGEMENT

The author would like to thank the Head of Pharmaceutical Chemistry Division, Gadjah Mada University for giving advice and facilities for this molecular modeling study. This research is supported by the Directorate of Higher Education Research and the Government of the Republic of Indonesia through the Health Research Grant.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors contributed extensively to the work presented in this paper.

CONFLICT OF INTERESTS

Declared none

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