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IN SILICO STUDY OF CEPHALOSPORIN DERIVATIVES TO INHIBIT THE ACTIONS OF *Pseudomonas aeruginosa*

Studi *In Silico* Senyawa Turunan Sefalosporin dalam Menghambat Aktivitas Bakteri *Pseudomonas aeruginosa*

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ABSTRAK

Infeksi yang diakibatkan oleh bakteri gram-negatif, seperti Pseudomonas aeruginosa *telah menyebar luas di seluruh dunia. Hal ini menjadi ancaman terhadap kesehatan masyarakat karena merupakan bakteri yang* multi-drug resistance *dan sulit diobati. Oleh karena itu, pentingnya pengembangan agen antimikroba untuk mengobati infeksi semakin meningkat dan salah satu yang saat ini banyak dikembangkan adalah senyawa turunan sefalosporin. Penelitian ini melakukan studi mengenai interaksi tiga dimensi (3D) antara antibiotik dari senyawa turunan Sefalosporin dengan* penicillin-binding proteins *(PBPs) pada* P. aeruginosa*. Tujuan dari penelitian ini adalah untuk mengklarifikasi bahwa agen antimikroba yang berasal dari senyawa turunan sefalosporin efektif untuk menghambat aktivitas bakteri* P. aeruginosa*. Struktur PBPs didapatkan dari Protein Data Bank (PDB ID: 5DF9). Sketsa struktur turunan sefalosporin digambar menggunakan Marvins Sketch. Kemudian, studi mengenai interaksi antara antibiotik dan PBPs dilakukan menggunakan program Mollegro Virtual Docker 6.0. Hasil yang didapatkan yaitu nilai* rerank score *terendah dari kelima generasi sefalosporin, di antaranya sefalotin (-116.306), sefotetan (-133.605), sefoperazon (-160.805), sefpirom (-144.045), dan seftarolin fosamil (-146.398).*

Keywords: *antibiotik, penicillin-binding proteins, P. aeruginosa, sefalosporin, studi interaksi*

ABSTRACT

Infections caused by gram-negative bacteria, such as *Pseudomonas aeruginosa*, have been spreading worldwide. It is a threat to public health because of its multi-drug resistance and difficulty to treat. Therefore, the demand for developing antimicrobial agents to treat infections is increasing. One of them that is currently under development is cephalosporin derivative compounds. This research studied the three-dimensional (3D) interaction between antibiotics from cephalosporin derivatives and penicillin-binding proteins (PBPs) in *P. aeruginosa*. This study aimed to clarify whether the cephalosporin derivatives were effective in inhibiting the activity of *P. aeruginosa*. The PBPs structure was obtained from the Protein Data Bank (PDB ID: 5DF9). The structural sketch of the cephalosporin derivative was drawn using the Marvins Sketch, whereas the study on the interaction between antibiotics and PBPs was carried out using the Mollegro Virtual Docker 6.0 program. The results showed the lowest rerank score from five cephalosporin derivatives, namely cephalotin (-116,306), cephotetan (-133.605), cephoperazone (-160.805), cephpirome (-144.045), and cephtaroline fosamil (-146.398).

Kata Kunci: antibiotics, cephalosporins, interaction study, PBP, *P. aeruginosa*

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INTRODUCTION

Infectious diseases are one of the leading causes of morbidity and mortality, and a decrease in the productivity of people, especially in developing countries. They are caused by bacteria that occur in communities or hospitals (Ahrens and Pigeot 2014; Golwalla et al. 2017), and the use of antibiotics is very important in preventing and eliminating them. However, over 70% pathogenic bacteria have become more resistant to multiple types of antibiotics. Multidrug-resistant (MDR) bacteria formally referred to as “superbugs” are the major causes of infections because of failure to respond to conventional treatment (Pisano et al., 2019). Besides, the inappropriate use of antibiotics in medicine have made some serious infections become more difficult to treat (Abrigach et al. 2018).

Gram-negative pathogens are often responsible for the four most frequent types of hospital-acquired infection. They include pneumonia, intra-abdominal infection (IAI), urinary tract infection (UTI), and bloodstream infection (BSI) (Merchant et al., 2018). One of the types of gram-negative bacteria that is dangerous because of its nature is the *Pseudomonas aeruginosa*. Furthermore, the treatment of infections caused by these resistant bacteria requires a high potential antibiotic. *P. aeruginosa* which is also referred to as an opportunistic pathogen which uses the damage of its host defense mechanism to initiate an infection. This type of bacteria adapts to challenging environments such as in the damaged lung of cystic fibrosis patients and also to the problems of the immune system and antibiotics treatment (Hogardt and Heesemann 2011, Brao et al., 2020).

The cell wall is an important structure for bacterial survival (An et al. 2015) and the membrane-binding enzyme involved in the final stages of bacterial cell wall synthesis is the Penicillin-binding Protein (PBP) (Sainsbury et al. 2011; An et al. 2015). These proteins are grouped based on their conserved domain structure and molecular weight (Kocaoglu et al. 2015). PBPs have been studied for a long period of time and have been chosen as the highly successful β-lactam antibiotics target (Macheboeuf et al. 2006). These antibiotics exert their antibacterial effect through covalent interactions with PBPs, thereby blocking the terminal step in cell wall biosynthesis (Kosowska-Shick et al. 2010). The levels of expression of PBPs differ between β-lactam resistant bacterial strains. However, this variation does not appear to be linked with the resistance development (Ren et al., 2016).

An example of an antibiotic that has the activity of inhibiting the growth of these bacteria is the Cephalosporin derivatives which are betalactam antibiotic that inhibits the synthesis of bacterial cell walls. Currently, there have been five generations of Cephalosporin derivatives that are active against gram-positive and gram-negative bacteria (Masoud et al. 2014). However, it is necessary to carry out further studies in order to determine the most potent antibiotic activity against *P. aeruginosa*.

Molecular docking study could be used to model the interaction of a small molecule and protein at the atomic level. Furthermore, it is used in characterizing the behaviour of small molecules’ at the binding site of target proteins and to elucidate fundamental biochemical processes (Meng et al. 2011). The definition of molecular docking is an optimization problem which describes the “best fit” orientation of a ligand that binds to a particular protein of interest. The Modes of Binding are several possible mutual conformations in which binding occur (Vijesh et al. 2013). Docking is an important tool in pharmaceutical research which requires a program that is based on a different algorithm. This technique is not a stand-alone method and requires the workflow of various experimental techniques in silico (Meng et al. 2011). Therefore, the aim of this study is to confirm the antimicrobial compounds from the cephalosporins generation that are effective in inhibiting the action of *P. aeruginosa*.

MATERIALS AND METHODS

This study was performed at the design and modelling laboratory in Centre of Pharmaceutical and Medical Technology BPPT (coordinates: -6.3572656, 106.6658068). Furthermore, the crystal structure of Penicillin-binding proteins (PBPs) was obtained from the Protein Data Bank (PDB ID: 5DF9). It was penicillin-binding protein 3 (PBP3) from *P. aeruginosa* that was

the molecular target of β-lactam based antibiotics(Berman et al. 2000; Kumar et al. 2014). The compounds were obtained from the study conducted by Masoud et al., (Masoud et al. 2014) and were the derivatives of cephalosporin from the first generation to the fifth generation. Cephalosporins are relatively nontoxic group of antibiotics (Gad 2014; Han et al. 2018) and are also one of the most frequently prescribed drugs. This is due to their wide-range and generally tolerated clinical uses, with approximately 1-3% of the population reporting cephalosporin allergies (Chaudhry et al. 2019). The 2D structures of ligands were drawn using *Marvin Sketch 19.16* and conformed into 3D structures. Furthermore, the 3D structure of ligand molecules were constructed, optimized, and converted into Mol2 file format (Lee and Jones 2018) of which the lowest energy structure was chosen. Docking simulation between antibiotics and PBPs were performed using the Mollegro Virtual Docker 6.0 program (Thomsen and Christensen 2006).

Docking studies

The structure of PBPs was obtained from the Protein Data Bank (Kumar et al. 2014) (http://www.rcsb.org) with a resolution of 2.7 Å. These studies were carried out to get the docking score and the interaction between cephalosporin derivative antibiotics with PBPs of bacteria. Validation method was conducted by extracting the ligands that were already present in the proteins before performing the docking processes (Firdayani et al. 2018). The programs that were able to return poses below a pre-selected Root Mean Square Deviation (RMSD) value from the known conformation (usually 1.5 or 2 Å depending on ligand size) were considered to have performed successfully (Hevener et al. 2009). The docking method was performed on the PBPs ligand in the coordinates with x, y, z values, namely -42.95; -9.10; -39.07 and radius 15 Å respectively. The docking parameter of the system was the grid resolution with 0.30 Å, using the MolDock SE algorithm with 10 number of runs. Maximum iterations used in this system was 1500 with a maximum population size of 50. Furthermore, after the docking of the PBPs ligand was carried out, that of the antibiotics molecule was then inserted into the system.

RESULT AND DISCUSSION

Taking coordinate space samples from the target binding site and assessing any possible ligand poses within these sites was required in the docking process. The RMSD value which is less than two indicates that this method was valid. Furthermore, the RMSD value that was obtained from this simulation was 0.99466. The structure from before and after molecular docking (MD) is shown in Figure 1.

The best binding poses for each ligand of antibiotics molecule were the those that had the lowest binding energy which are represented by negative docking scores. Furthermore, the result of the docking scores were analyzed into Table 1.

The rerank score is a parameter that is often used to analyze the interaction between a drug and its receptor because it is more complete than the Moldock score. It is a linear combination of the E-inter between ligand and protein and the E-intra from the ligand (Singh et al. 2016). The data revealed that the cephalosporin derivatives had antibiotic effect against *P. aeruginosa* that were represented by the negative values of rerank score. Furthermore, the lowest rerank scores from the first generation to the fifth generation, include cephalotin (-116.306), cefotetan (-133.605), cefoperazone (-160.805), cefpirome (-144.045), and ceftarolinefosamil (-146.398). The hydrogen bond interactions between the antibiotics and PBPs of *P. aeruginosa* are shown in Figure 2.

Our data revealed that cefoperazone was the best antibiotic against *Pseudomonas aeruginosa* which was used in this study with a rerank score of -160.805. The relationship with the residue of the lower rerank score

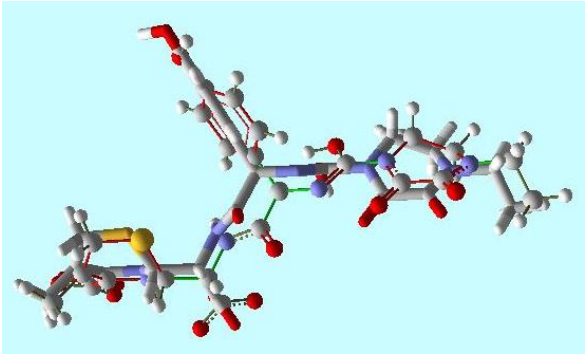

Figure 1. Redocking position of reference ligand in Penicillin-binding Proteins (PBPs)

Table 1. Molecular docking result

Generation	Ligand	MolDock Score	Rerank Score	HBond	Interaction
First	Cephalotin	-144.592	-116.306	-12.6475	Ser294, Thr487, Ser485
	Cefaloridine	-138.571	-116.276	-8.26248	Lys484, Ser349, Ser294, Thr487
	Cefazolin	-138.787	-113.67	-12.3866	Gly535, Thr487, Ser485, Gly534
	Cefapirin	-137.94	-109.759	-17.9191	Tyr409, Thr487, Asn351, Ser349, Ser294
	Cefroxadine	-115.849	-104.879	-11.5072	Tyr409, Thr487, Ser294, Ser349
	Cefradine	-111.313	-101.25	-11.8415	Tyr409, Thr487, Ser349, Ser294
	Cefadroxil	-112.962	-101.241	-16.7688	Ser349, Asn351, Thr487, Arg331, Tyr407, Tyr409
	Cephalexin	-105.981	-91.8439	-10.4703	Arg331, Thr329, Tyr409, Arg489, Asn351
Second	Cefotetan	-164.679	-133.605	-11.0131	Arg489, Thr329, Tyr409, Asn351, Gly535, Ser485, Thr487, Ser349, Ser294
	Cefotiam	-154.443	-124.411	-11.7498	Ile347, Thr487, Arg331, Arg489, Tyr409
	Cefminox	-143.174	-124.375	-18.4823	Arg489, Ser485, Ser349, Lys484, Ser294, Asn351, Thr487, Tyr409, Tyr407
	Cefamandole	-149.519	-123.774	-22.7464	Asn351, Ser349, Ser294, Thr487, Ser485, Gly535
	Cefonicid	-152.638	-123.628	-16.5122	Ile347, Ser334, Val333, Thr487, Ser349, Ser294, Tyr409, Arg 489
	Cefoxitin	-136.803	-118.587	-14.7191	Ser485, Tyr409, Ser294, Thr487, Ser349
	Cefuroxime	-138.464	-114.255	-9.40136	Arg489, Tyr409, Thr487, Asn351
	Ceforanide	-154.466	-113.816	-7.40938	Arg331, Arg489, Asn351
	Cefmetazole	-138.425	-112.959	-10.6955	Thr487, Tyr409, Arg489, Ser349, Ser294
	Cefprozil	-110.591	-102.499	-8.18848	Ser349, Ser294, Tyr409
	Cefaclor	-109.995	-100.268	-18.5491	Tyr409, Thr487, Ser249, Ser485, Ser349, Lys484, Asn351

Table 1. Molecular docking result (continued)

Generation	Ligand	MolDock Score	Rerank Score	HBond	Interaction
Second	Loracarbef	-112.341	-97.6982	-12.9883	Thr487, Asn351, Ser294, Ser485, Ser349
Third	Cefoperazone	-194.788	-160.805	-24.9446	Arg489, Tyr409, Tyr407, Arg331
	Cefsulodin	-173.407	-139.393	-14.619	Thr487, Ser349, Ser294, Ser485
	Cefodizime	-167.642	-135.185	-15.7511	Tyr409, Ser294, Arg489, Thr487, Arg331, Arg499
	Ceftazidime	-157.452	-127.854	-8.60214	Tyr409, Arg489, Asn351, Tyr407
	Cefotaxime	-151.61	-125.827	-17.8636	Arg489, Ser485, Ser294, Lys484, Ser349, Thr487, Asn351, Tyr409
	Cefditoren	-157.005	-124.507	-10.4001	Asn351, Ser334, Ser349, Ser294, Thr487, Tyr409
	Ceftiofur	-164.475	-124.036	-13.2387	Ser294, Arg489, Thr487, Tyr409, Ser349, Ser485
	Ceftriaxone	-165.97	-124.033	-8.93295	Tyr407, Arg489
	Cefixime	-156.815	-123.404	-21.9007	Tyr532, Arg489, Tyr409, Ser349, Lys484, Ser294, Thr487, Asn351
	Cefpodoxime	-143.688	-120.741	-12.2727	Thr487, Tyr409, Asn351, Arg489
	Ceftibuten	-140.812	-118.684	-13.1578	Asn351, Ser349, Ser294, Ser485, Thr487
	Cefetamet	-133.743	-116.248	-13.9804	Ser485, Thr487, Ser294, Ser349, Tyr409, Arg489
	Ceftizoxime	-134.105	-111.873	-17.0225	Ser485, Arg489, Tyr409, Thr487, Asn351, Ser294, Ser349
	Cefdinir	-122.104	-111.17	-15.1259	Arg489, Ser294, Ser349, Ser485, Asn351, Thr487
Fourth	Cefpirome	-173.913	-144.045	-11.7015	Asn351, Tyr409, Ser294, Thr487, Gly535, Gly534, Ser485
	Cefepime	-170.398	-135.567	-14.0559	Ser485, Ser349, Ser294, Thr487, Asn351, Tyr409
	Cefquinome	-149.411	-120.689	-9.39701	Asn351, Ser294, Thr487, Ser349
Fifth	Ceftaroline Fosamil	-185.78	-146.398	-14.2219	Tyr407, Arg331, Tyr503, Arg489, Glu500
	Ceftobiprole	-166.403	-136.283	-7.71285	Ser294, Ser485, Tyr407, Arg489, Ser349, Thr487

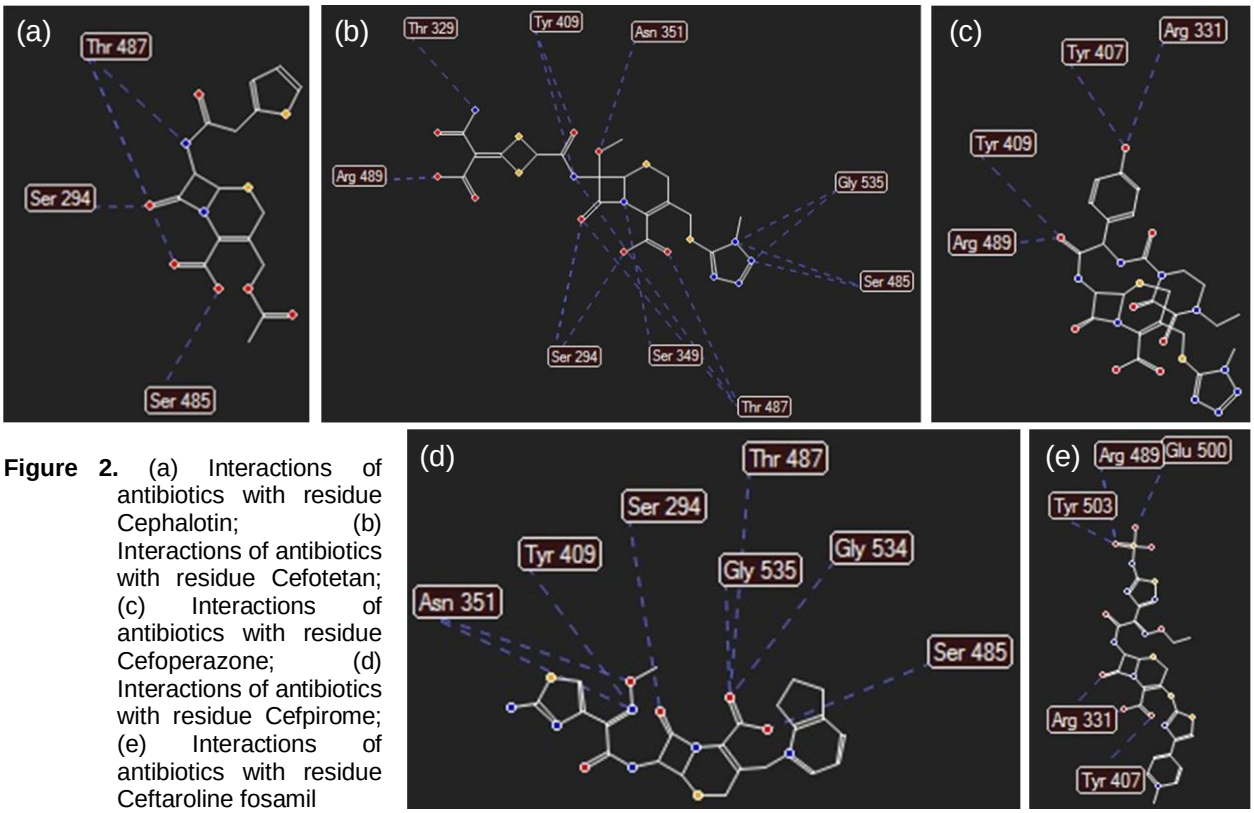

Figure 2. (a) Interactions of antibiotics with residue Cephalotin; (b) Interactions of antibiotics with residue Cefotetan; (c) Interactions of antibiotics with residue Cefoperazone; (d) Interactions of antibiotics with residue Cefpirome; (e) Interactions of antibiotics with residue Ceftaroline fosamil

shows that the interaction between the drug and receptor is more stable. The hydrogen bonds of cefoperazone interaction with PBPs was with Arg489, Tyr409, Tyr407, Arg331. Based on the result, it was predicted that cefoperazone has good activity against PBPs of *P. aeruginosa* bacteria. This is in accordance with the study conducted by Ren et al.(2016) which states that cefoperazone is one of the few cephalosporins that are effective in treating *Pseudomonas* bacterial infections. However, cefoperazone could inhibit carbapenem-resistant *P. aeruginosa* due to the MIC values, which are between the ranges of 4 to 64 µg/mL (Lai et al. 2019).

CONCLUSION

The molecular docking studies were performed to explore possible binding modes of cephalosporin derivatives into PBPs of bacteria. The study revealed that cephalosporin derivatives have good activity against bacteria especially the third generation. Furthermore, cefoperazone showed the lowest value of rerank score and was proven to be effective in inhibiting the actions of *P. aeruginosa bacteria*.

AUTHORSHIP STATEMENT

All authors had an equal contribution in conducting the research, preparing, and revising the manuscript.

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