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Original Article

Hansch analysis by QSAR model of curcumin and eight of its transformed derivatives with antimicrobial activity against *Staphylococcus aureus*

[Análisis Hansch mediante modelo QSAR de curcumina y ocho de sus derivados transformados con actividad antimicrobiana contra *Staphylococcus aureus*]

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Abstract

Context: In the last decade, antimicrobial resistance cases have been widespread. The discovery and development of new drugs need to be done to overcome the case. Some research has found that some compounds, which are curcumin transformation derivatives, are able to inhibit the growth of *Staphylococcus aureus*.

Aims: To evaluate the development of antimicrobial candidates of curcumin versus *S. aureus*.

Methods: The *in silico* approach method, along with the QSAR technique, plays an important role in the process of discovery and development of new drugs. In this study, we focused on developing curcumin transformation derivatives that are much more potent by making the best QSAR equation of curcumin and eight curcumin transformation derivatives that have been tested *in vitro* for their antimicrobial activity against *Staphylococcus aureus*.

Results: The best QSAR equation was obtained from curcumin transformation derivatives as antimicrobial activity against *S. aureus*, with pMIC = 0.812 (± 0.162)EHOMO +5.443 (± 1.659) (n = 9; Sig = 0.002; R = 0.884; R^2 = 0.782; F = 25.153; Q^2 = 0.57.

Conclusions: In this study, an increase in the antimicrobial activity of curcumin transformation derivatives against *S. aureus* by increasing EHOMO was observed. The best QSAR equation can be a tool to obtain a more potential new chemical structure model and reduce trials and errors.

Keywords: antibacterial; curcumin; molecular docking; QSAR; transformation.

Resumen

Contexto: En la última década se han generalizado los casos de resistencia a los antimicrobianos. Es necesario descubrir y desarrollar nuevos fármacos para superar el caso. Algunas investigaciones han descubierto que algunos compuestos, que son derivados de la transformación de la curcumina, son capaces de inhibir el crecimiento de *Staphylococcus aureus*.

Objetivos: Evaluar el desarrollo de candidatos antimicrobianos de la curcumina contra *S. aureus*.

Métodos: El método de aproximación *in silico* con la técnica QSAR desempeña un papel importante en el proceso de descubrimiento y desarrollo de nuevos fármacos. En este estudio, nos centramos en el desarrollo de derivados de transformación de la curcumina que sean mucho más potentes realizando la mejor ecuación QSAR de la curcumina y ocho derivados de transformación de la curcumina que han sido probados *in vitro* por su actividad antimicrobiana contra *S. aureus*.

Resultados: Se obtuvo la mejor ecuación QSAR de los derivados de transformación de la curcumina como actividad antimicrobiana contra *S. aureus*, con pMIC = 0,812 (± 0,162)EHOMO +5,443 (± 1,659) (n = 9; Sig = 0,002; R = 0,884; R2 = 0,782; F = 25,153; Q2 = 0,57.

Conclusiones: En este studio se observó un aumento de la actividad antimicrobiana de los derivados de transformación de curcumina frente a *S. aureus* mediante el aumento de EHOMO. La mejor ecuación QSAR puede ser una herramienta para obtener un nuevo modelo de estructura química más potencial y reducir los ensayos y errores.

Palabras Clave: antibacteriano; curcumina; acoplamiento molecular; QSAR; transformación.

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INTRODUCTION

Staphylococcus aureus is an opportunistic gram-positive bacterium that often infects skin and upper respiratory tract infections in humans. Some infections caused by *Staphylococcus aureus* include septic shock (56%), pneumonia (32%), endocarditis (19%), bacteremia (10%), and cellulitis (6%) (Green et al., 2012). Methicillin is a beta-lactam antibiotic that is very sensitive for testing resistance in *Staphylococcus aureus*. Methicillin is only used *in vitro* and is not widely used clinically because methicillin has strong nephrotoxic side effects. In the last decade, many cases of *Staphylococcus aureus* reported were resistant to methicillin or are called methicillin-resistant *Staphylococcus aureus* (MRSA) (Green et al., 2012; Larsen et al., 2022; Mun et al., 2014).

To resolve the problem of MRSA cases, many researchers synthesize new compounds or use phytochemicals to find compounds that have more potential against MRSA with minimal side effects (Boehlich et al., 2020; Masumi et al., 2022; Mun et al., 2014; Zhang et al., 2018). The phytochemical that was very popularly used is curcumin (Mun et al., 2014). Curcumin is a major phytochemical often found in *Curcuma longa* L. or *Curcuma domestica* Valeton (*Zingiberaceae* family) (Teow et al., 2016). Various pharmacological activities of curcumin have been widely reported, including its antimicrobial, antidiabetic, anti-inflammatory, anticancer, and antioxidant activity (Teow et al., 2016).

In terms of antibacterial activity, curcumin has been reported to affect several bacteria, such as *Staphylococcus aureus*, *Trichophyton gypseum*, *Salmonella paratyphi*, and *Mycobacterium tuberculosis* (Schraufstatter and Bernt, 1949). Curcumin has great potential against MRSA (Mun et al., 2014). The weakness of curcumin, which was easily degraded due to the presence of a double H-alpha ketone group that can undergo keto-enol tautomeric and then undergo autoxidation to become bicyclopentadione derivative, as shown in Fig. 1 (Gordon et al., 2015; Schiener et al., 2015). Therefore, several studies have attempted to close the H-alpha biketone functional group in curcumin into a closed ring structure so that it is made much stronger and has the potential to against MRSA (Hamed et al., 2013; Teow et al., 2016).

MRSA resists beta-lactam antibiotics due to its low binding affinity to the penicillin-binding protein receptor penicillin-binding protein 2a (PBP2a) encoded by the mecA gene determinant. MRSA requires the mecA gene to reduce the sensitivity of the PBP2a receptor to beta-lactam antibiotics (Masumi et al., 2022; Teow et al., 2016). Therefore, this research focuses on an *in silico* study of several curcumin derivatives designed through the QSAR process on the PBP2a receptor (PDB ID: 4DKI) (Hamed et al., 2013; Lovering et al., 2012; Putra et al., 2023).

MATERIAL AND METHODS

QSAR procedure

The QSAR procedure that was conducted in this study was through ligand-based drug design (LBDD). This study used three processes to obtain the best QSAR equation, namely first collecting molecular descriptor data from various software. The second is to perform multivariate analysis through the multiple linear regression (MLR) method, Pearson correlation, and Z value, along with the determination of the best QSAR equation by internal validation method (r, R^2, F, sigma, Q^2) (Gramatica 2007; Putra et al., 2023). Finally, after obtaining the best QSAR equation, it is then used to design a new, more potential compound model and *in silico* study for pharmacokinetic prediction (ADMET) as well as molecular docking was redone on *Staphylococcus aureus* PBP2a (PDB ID: 4DKI) (Lovering et al., 2012). The research scheme is shown in Fig. 2.

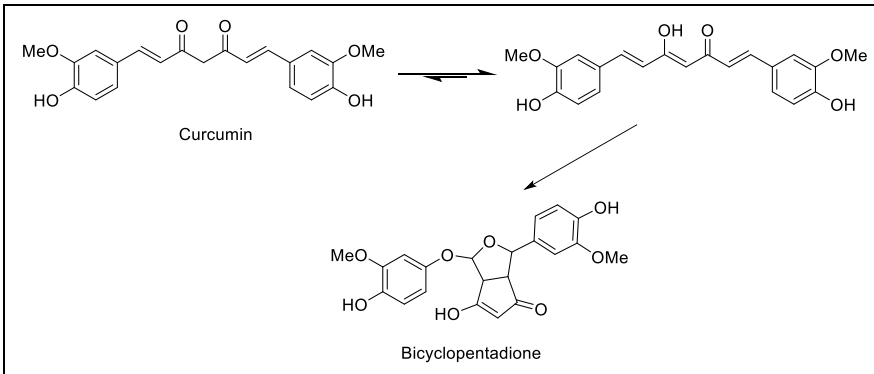


Figure 1. Degradation of curcumin becomes bicyclopentadione derivatives.

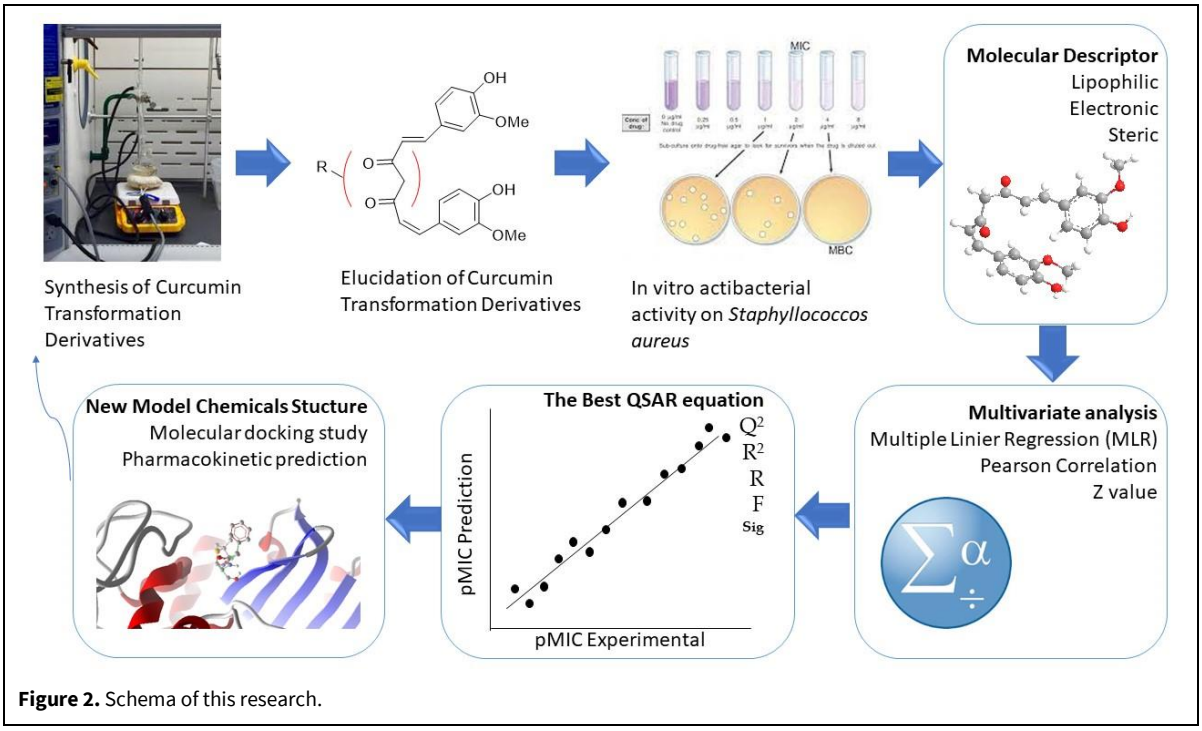


Figure 2. Schema of this research.

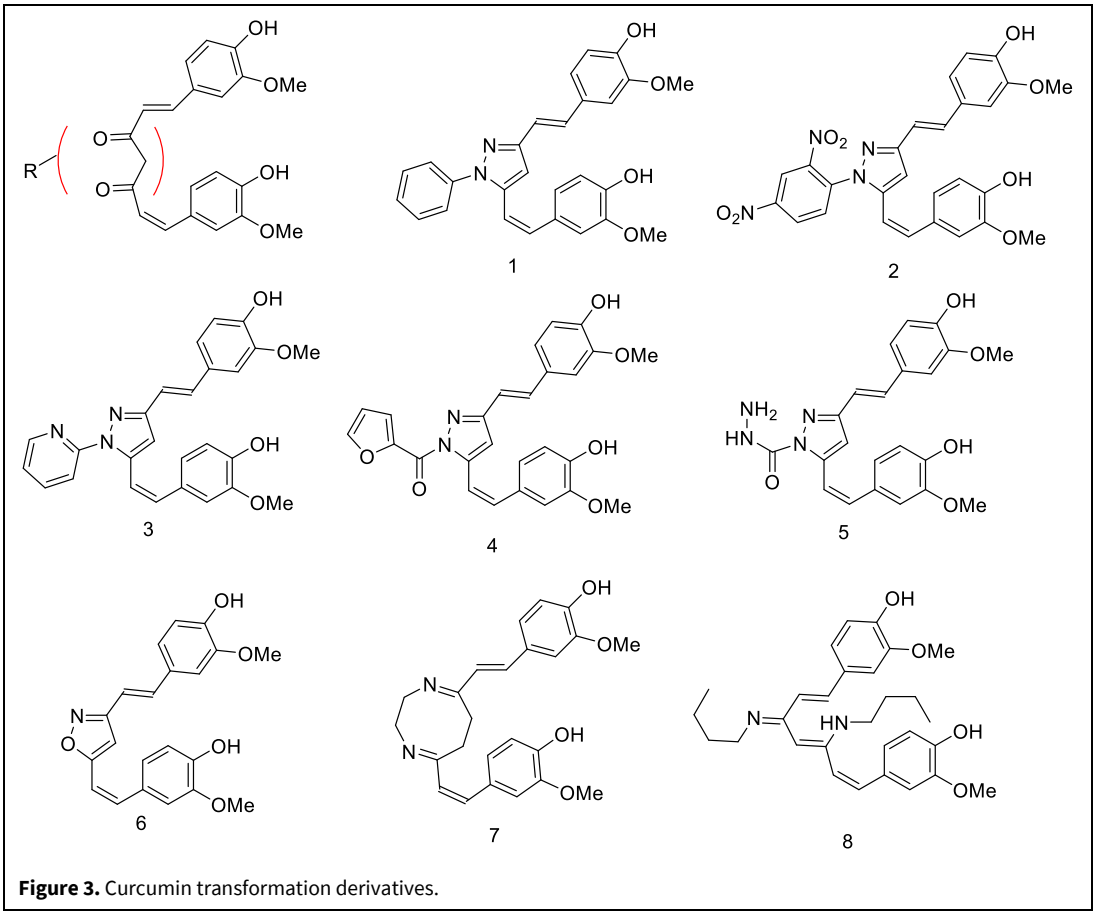


Figure 3. Curcumin transformation derivatives.

Collection of molecular descriptors

Eight compounds were derived from curcumin transformation (Fig. 3) that have been synthesized and tested for their antibacterial activities against *S. aureus* (Hamed et al., 2013). It was drawn in 2D and 3D using the Chembiodraw application. These eight compounds have been successfully synthesized and *in vitro* antibacterial activities in previous research (Hamed et al., 2013). The QSAR equation obtained from pMIC that has been obtained from the antibacte-

rial against *S. aureus* is equated with various descriptors obtained from the Chembiodraw and pkCSM applications. Descriptors used represent several Hansch QSAR parameters, which are grouped based on three parameters: hydrophobic, electronic, and steric (Hansch and Fujita, 1964; Jhanwar et al., 2011; Kubinyi, 1993).

Multivariate analysis and validation of the QSAR equation

The search for the best equation model used variables depending on the growth inhibition activity of *S. aureus* (log 1/MIC or -log MIC or pMIC) from the results of the previous experiments (Hamed et al., 2013). Independent variables were used in the form of descriptor values representing three parameters: lipophilic, electronic, and steric. All variables were analyzed using the MLR method by initial screening by applying the Pearson correlation or Matrix correlation method using SPSS software. The results obtained were in the form of QSAR equations and statistical parameter values such as the values of r, R^2, and F (Putra et al., 2023).

The value of F indicated the significance of the relationship when compared to the F table. The value of F was an indicator of the number to show that the relationship, expressed by the obtained equation, was true and not a coincidence. The value of r (correlation coefficient) indicated the level of relationship between the biological activity data of experimental observations and the data of calculation results based on equations obtained from regression analysis. A greater value of r counts than the r table showed a stronger relationship between the biological activity data and experimental observations. The value of R^2 (coefficient of determination) indicated the percentage of biological activity that can be explained in relation to the parameters of physical-chemical properties or descriptors used. A greater value of R^2 counted than the R^2 table showed a strong percentage relationship of biological activity with the descriptor used.

To obtain the model with the highest r value, the elimination of the compound that had the greatest deviation based on the value of Z in the computation results was conducted, where the structure of the compound with a value of Z >2 was eliminated from the statistical calculation. In addition to these statistical parameters, the calculation results also obtained the constant and coefficient values of each independent variable involved in the resulting equation. The obtained coefficient value was used to calculate the activity of theoretical inhibition.

The best QSAR equation was validated with several parameters. There were Fischer criteria (F), coefficient of determination (R^2) >0.6, cross-validation coefficient or leave one out (Q^2) >0.5, and difference between R^2 and Q^2 ≤0.3 (Adeniji et al., 2018; Chirico and Gramatica, 2011; Gramatica 2007; Putra et al., 2023). These parameters were calculated based on the following formulas [1] and [2].

$$R^2 = 1 - \left[\frac{\sum(Y_{exp} - Y_{Pred})^2}{\sum(Y_{exp} - \bar{Y}_{training})^2}\right] \quad [1]$$

$$Q^2 = 1 - \left[\frac{\sum(Y_{pred} - Y_{exp})^2}{\sum(Y_{exp} - \bar{Y}_{training})^2}\right] \quad [2]$$

Where Y_{exp}, Y_{pred}, and $\bar{Y}_{training}$ are experimental activity, the predicted activity, and the mean experimental activity of the samples in the training set, respectively.

New models of chemical structure

The best QSAR equation obtained was used to find a better compound candidate by taking into account the pMICpred value. Molecular docking analysis was redone, ADMET prediction using MVD along with pkCSM online as a feasibility screening process to be synthesized was conducted, and *in vitro* test was also redone on some compound candidates.

In the molecular docking study, we used the software Molegro Virtual Docker (MVD) Ver. 5 with PBP2a receptor as the main target, which was downloaded from the data bank on the website https://www.rcsb.org/ with the PDB ID: 4DKI (Lovering et al., 2012). The PBP2a structure was obtained through X-ray diffraction from receptor isolates found in *Staphylococcus aureus* subsp. *aureus* COL (Lovering et al., 2012). The validation process involved redocking the native ligand, ceftobiprole, which is a clinically commonly used standard drug in lung cancer cases. The acceptance criterion for the validation process was an RMSD value of <2 Å (Putra et al., 2016; Thomsen and Christensen, 2006).

The new compound design was created using the 2D drawing feature in Chembiodraw version 11 software. The 2D chemical structure was then converted into a 3D ligand using Chembio3D version 9 software. The 3D chemical structure underwent a minimal energy calculation using the MMFF94 calculation method, and the ligand was saved as a PDB file (Thomas, 1996). This file was then imported into the MVD application to obtain rerank scores, which represent the free energy of interaction between the ligand and the receptor (Putra et al., 2016; Thomsen and Christensen, 2006). To predict the pharmacokinetic profile data, the compound design file was entered into the online SCF Bio application (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) to obtain predicted values for the Lipinski rule and pkCSM

(https://biosig.lab.uq.edu.au/pkcsm/prediction), and also SIB online (http://www.swissadme.ch/index.php) to obtain data on absorption, distribution, metabolism, excretion, and toxicity predictions, the file was submitted to an application that could provide such data (Daina et al., 2017; Jayaram et al., 2013; Pires et al., 2015; Suhud et al., 2019).

RESULTS

Descriptor identification results of curcumin and eight curcumin transformation derivatives

The descriptor used represented several Hansch QSAR parameters, consisting of three parameters: hydrophobic, electronic, and steric (Jhanwar et al., 2011; Kubinyi, 1993; Putra et al., 2023; Todeschini and Consonni, 2009). Lipophilic parameters were Log P, Clog P, and Log S; electronic parameters were TPSA, EHOMO, ELUMO; while steric parameters were molar refractivity (MR), molecular weight (Mr), and molecular volume (MV). The descriptor results of lipophilic, electronic, and steric parameters are shown in Table 1.

Results of multivariate analysis and QSAR equation validation

To obtain the best correlation between pMIC (Y axis) and several descriptors (X axis), screening was used applying the Pearson correlation or Matrix correlation method, which was then carried out by MLR (Putra et al., 2023; Soni et al., 2009; Verma et al., 2017). The Pearson correlation or Matrix correlation results can be seen in Table 2. Descriptors with a meaningful relationship with pMIC can be seen from results close to 1 or -1. The descriptors included in the QSAR equation were only one because the number of compounds made from this equation is only n = 9. One descriptor parameter can enter the QSAR equation with the number n = 5 (Topliss and Costello, 1972). From the Matrix correlation table results, which still meet the requirements, the electronic parameter is represented by EHOMO with a value of 0.884.

The QSAR equation of screening matrix correlation is created and compared with several other QSAR equations for the MLR process. MLR process was carried out by analyzing the Fischer criteria (F), coefficient of determination (R^2), and cross-validation coefficient by leaving one out (Q^2) with the results in Table 3.

Based on MLR analysis of four QSAR equations, only QSAR equation [1] met the requirements of the validation criteria. These were a coefficient of determination (R^2) >0.6, a cross-validation coefficient or leave one out (Q^2) >0.5, and a difference between R^2 and $Q^2 \leq 0.3$ (Putra et al., 2023). The best QSAR equation was equation 1, pMIC = 0.812 (± 0.162) EHOMO + 5.443 (± 1.659) with sig, r, R^2, F and Q^2 values that have met the requirements criteria (Adeniji et al., 2018; Chirico and Gramatica, 2011; Hardjono et al., 2016, Luo et al., 2012; Putra et al., 2023). The Z score between pIC_{50} experimental and pIC_{50} prediction was also nothing more than 2, which can be seen in Table 4 and Fig. 3.

Table 1. Descriptors of lipophilic, electronic and steric parameters of curcumin and its transformation derivatives.

Compound	Y axis	X axis								
	pMIC	Lipophilic			Electronic			Steric		
		Log P	ClogP	Log S	TPSA	EHOMO	ELUMO	MR	Mr	MV
Curcumin	-3.988	3.15	2.25	-4.20	93.06	-11.03	-5.29	102.80	368.38	156.53
1	-3.280	5.21	5.94	-6.91	76.74	-10.61	-3.03	131.33	440.49	191.84
2	-3.225	5.02	5.68	-7.70	168.38	-10.54	-4.02	148.98	530.49	221.14
3	-2.685	4.60	4.87	-6.56	89.63	-9.68	-3.14	129.13	441.48	191.06
4	-2.687	4.50	5.92	-5.93	106.95	-10.81	-4.74	128.43	458.46	195.16
5	-2.726	2.65	2.77	-4.82	131.86	-10.41	-2.91	117.36	422.43	178.17
6	-3.380	4.01	3.87	-5.12	84.95	-10.92	-3.59	104.27	365.38	156.14
7	-1.169	3.54	3.63	-4.56	83.64	-8.47	-2.35	128.73	406.47	176.09
8	-2.629	6.14	6.28	-6.84	83.31	-9.44	-3.43	146.87	478.62	208.88

TPSA: total polarity surface area; RS: rerank score; MR: molar refractivity; Mr: molecular weight; Mv: molecular volume.

Table 2. Person correlation or Matrix correlation of PIC_{50} with its various descriptors.

Descriptor	pMIC	Log P	ClogP	LogS	TPSA	EHOMO	ELUMO	MR	Mr	MV
pMIC	1									
Log P	-0.028	1								
ClogP	0.091	0.924	1							
LogS	0.109	0.852	-0.880	1						
TPSA	-0.147	-0.124	0.016	-0.304	1					
EHOMO	0.884	0.136	0.086	0.013	-0.265	1				
ELUMO	0.682	0.036	0.064	-0.076	-0.197	0.695	1			
MR	0.358	0.750	0.797	-0.823	0.321	0.433	0.267	1		
Mr	0.121	0.655	0.756	-0.862	0.587	0.131	0.038	0.930	1	
MV	0.172	0.727	0.812	-0.884	0.470	0.207	0.100	0.963	0.990	1

Table 3. Multiple linear regression of QSAR equations.

Equation number/name	QSAR equation					
(1)	pMIC = 0.812 (± 0.162) EHOMO + 5.443 (± 1.659)					
EHOMO	n = 9	Sig = 0.002	r = 0.884	R^2 = 0.782	F = 25.153	Q^2 = 0.57
(2)	pMIC = 0.570 (± 0.231) ELUMO - 0.805 (± 0.859)					
ELUMO	n = 9	Sig = 0.043	r = 0.682	R^2 = 0.465	F = 6.080	Q^2 = -0.02
(3)	pMIC = 0.069 Log S (± 0.239) -2.458 (± 1.422)					
Log S	n = 9	Sig = 0.780	r = 0.109	R^2 = 0.012	F = 0.084	Q^2 = -3.36
(4)	pMIC = 0.017 MR (± 0.017) -5.039 (± 2.159)					
MR	n = 9	Sig = 0.344	r = 0.358	R^2 = 0.128	F = 1.030	Q^2 = -0.43

Table 4. Difference of pIC_{50} experimental and pIC_{50} prediction.

Compound	pIC_{50} Experimental	pIC_{50} Prediction	Residues (Z score)
Curcumin	-3.988	-3.526	0.462
1	-3.280	-3.186	0.094
2	-3.225	-3.125	0.100
3	-2.685	-2.428	0.257
4	-2.687	-3.346	-0.659
5	-2.726	-3.017	-0.290
6	-3.380	-3.437	-0.058
7	-1.169	-1.448	-0.279
8	-2.629	-2.234	0.395

Determination of new compound design

From the QSAR equation, to obtain a more potent compound with a lower IC_{50} or a greater pMIC value, it is necessary to design a compound with criteria greater than EHOMO than compound 7. This means that to increase the value of the EHOMO/energy highest occupied molecular orbital, reducing the number of conjugated double bonds is advisable.

Compound 7 with experimental pMIC values and the largest prediction pMIC are used as reference standards to find candidates for more potent compounds. From the analysis of the EHOMO criteria, we would get a new compound design. Those were three

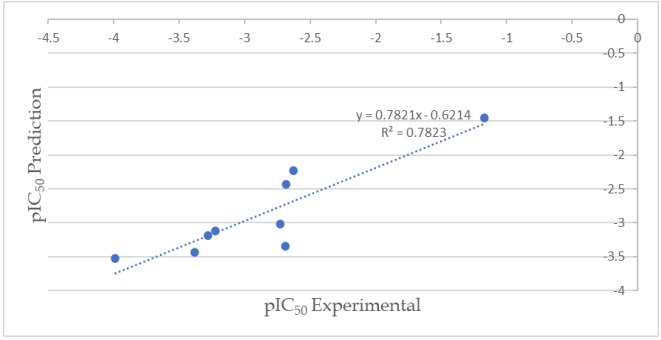
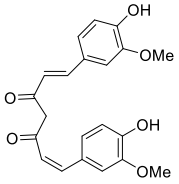
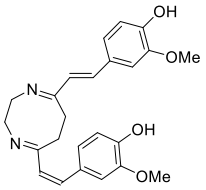
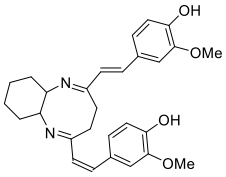
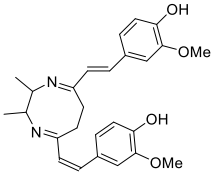
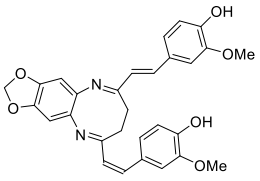


Figure 3. Regression between pIC_{50} experimental and pIC_{50} prediction.

Table 5. Descriptor and pIC_{50} prediction of new model chemicals structure.

Compound	EHOMO	pMIC prediction
 Curcumin	-11.03	-3.988
 Compound 7	-8.47	-1.445
 New 1	-7.98	-1.047
 New 2	-8.17	-1.201
 New 3	-8.19	-1.217

candidate compounds suitable for re-synthesizing, which were code-named New 1-3. The EHOMO results of compound 4 and New 1-3 compounds can be seen in Table 5.

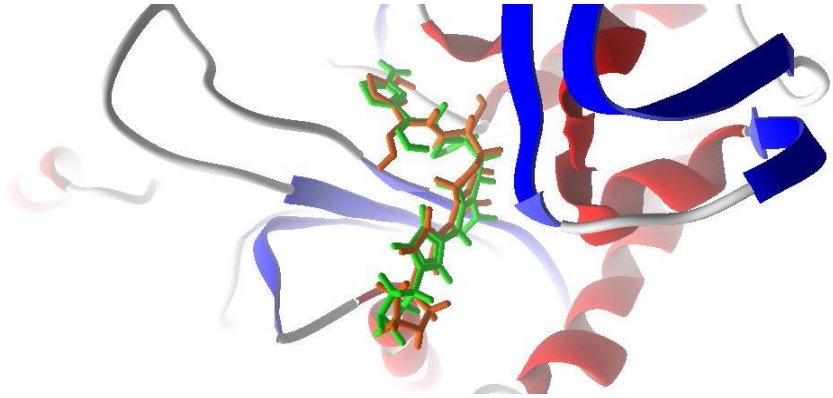


Figure 4. Comparison of the native ligand (Ceftobiprole) (green) with the docking result simulation (orange) by Molegro Virtual Docker (MVD) Ver.5.5 with RMSD of 1.19 Å.

Molecular docking study and ADMET prediction of new compound design

New 1-3 were prepared as ligands by drawing them in two dimensions in Chembiodraw version 11 software. The 2-dimensional ligand was then converted into the 3-dimensional ligand in Chembio3D version 11 software. The 3-D ligand performs the most stable minimal energy calculation by means of the MMFF94 calculation, and the ligand is stored in the PDB file type. (Thomas, 1996).

The receptors *S. aureus* PBP2a (PDB ID: 4DKI) were obtained from the Protein Data Bank (PDB) with PDB ID: 4DKI, which was re-prepared with Molegro Virtual Docker (MVD) Ver.5.5 (Lovering et al., 2012). PBP2a and its comparison ligand ceftobiprole were re-docked to validate the Molegro Virtual Docker (MVD) Ver.5.5. Therefore, it was used to dock the New 1-3 compounds.

Redocking aims to validate the downloaded PBD files and the software used for the New 1-3 compounds docking method to obtain valid and correct results. The redocking acceptance parameter is the root mean square deviation (RMSD) value <2.0 Å.

The grid box binding site was set X = 29.35 Å; Y = 30.01 Å; Z = 86.82 Å with a cavity surrounded by 27 amino acids. They were Gly 402, Ser 403, Lys 406, Lys 430, Tyr 446, Glu 447, Glu 460, Ser 462, Asp 463, Asn 464, Tyr 519, Gly 520, Gln 521, Lys 581, His 583, Asp 586, Lys 597, Ser 598, Gly 599, Thr 600, Ala 601, Glu 602, Met 605, Met 641, Ala 642, Ser 643, and Lys 647. The result of the redocking validation process with RMSD 1.19 Å is shown in Fig. 4. Hence, these results indicate that the method is valid for the docking test of the tested compound since the RMSD obtained is less than 2 Å (Sulistyowaty et al., 2023). The RMSD value showed the compatibility of the ligand coordinates from the crystallographic results compared to the ligand coordinates, which was redocked ceftobiprole on PBP2a of 1.19 Å, which is in accordance with the criteria of the docking process (Fig. 4).

Based on the docking result, a rerank score was obtained and interpreted as the prediction of the bond interaction between the drug and the receptor. The smaller the rerank score, the greater the degree of compatibility between the ligand and the receptor. The docking results can also be visualized and interpreted to provide an overview of the interaction of ligand bonds with receptors, including hydrogen bond interactions, hydrophobic interactions, and electronic interactions (Table 6 and Fig. 5).

The result of the rerank score of New 1-3 compounds proved to be lower than its native ligand, ceftobiprole (-69.74 kcal/mol), and reference drug standard for MRSA, methicillin (-79.31 kcal/mol). Based on the value of the rerank score, if it were arranged from the lowest to the highest energy, a rerank score was obtained as follows: New1<New2 <New3<methicillin<ceftobiprole. The presence of unconjugated ring such as cyclopentane at chemical structure New 1 caused higher EHOMO and made it a suitable interaction with PBP2a than chemical structure New 2 and New 3.

Based on the results of ADMET prediction using SCFBIO software, New 1-3 compounds adhere to Lipinski's Rule of Five criteria, which encompass Log P <5; Hydrogen Bond Donors (HBD) ≤5; Hydrogen Bond Acceptor (HBA) ≤5; MR 40-130 Å; Mr ≤500. Therefore, based on this prediction, these were predicted that New 1-3 compounds would be absorbed through the gastrointestinal tract (GIT) (Jayaram et al., 2013; Sulistyowaty et al., 2021). However, absorption predictions based on Lipinski's rule of five for ceftobiprole and methicillin fall outside of the criteria. As a result, ceftobiprole and methicillin are not formulated for clinical use in oral dosage forms, and both are only available in intravenous (IV) injection

Table 6. The Molecular docking result of ceftrobiprole, methicillin, compound 7, and New 1-3 compounds into active site *Staphylococcus aureus* penicillin-binding protein 2a.

Compound	Rerank score (kcal/mol)	Hydrogen bond	Steric interaction	Electronic interaction
Ceftobiprole	-69.74	Ser 403; Lys 406; Ser 462; Tyr 519; Ln 521; Ser 598; Thr 600; Ala 601	Ser 403; Lys 406; Ser 462; Tyr 446; Asn 464; Tyr 519; Gly 520; Gly 521; Ser 598; Gly 599; Thr 600; Ala 601; Glu 602	Lys 597
Methicillin	-79.31	Ser 403; Lys 406; Ser 462; Asn 464; Gly 521; Thr 600	Gly 402; Ser 403; Lys 406; Ser 462; Asn 464; Tyr 519; Gln 521; Thr 600	Lys 597
Compound 7	-102.50	Ser 403; Ser 462; Asn 464; Thr 600; Glu 602	Ser 403; Tyr 446; Ser 461; Ser 462; Asn 464; Thr 600; Glu 602; Gly 613	-
New 1	-125.81	Ser 400; Glu 447	Glu 402; Glu 447; Ser 461; Asn 464; Tyr 519; Ala 601	-
New 2	-116.99	Ser 403; Glu 447; Thr 600; Ile 614	Gly 402; Ser 403; Glu 447; Ser 461; Asn 464; Gln 521; Gly 599; Thr 600; Ala 601; Ile 614; Trp 616	-
New 3	-107.77	Ser 403; Glu 447; Ser 461; Asn 464; Thr 600; Ala 642; Ser 643	Ser 403; Tyr 446; Glu 447; Ser 461; Ser 462; Asn 464; Gln 521; Ser 598; Thr 600; Met 641; Ala 642; Ser 643	

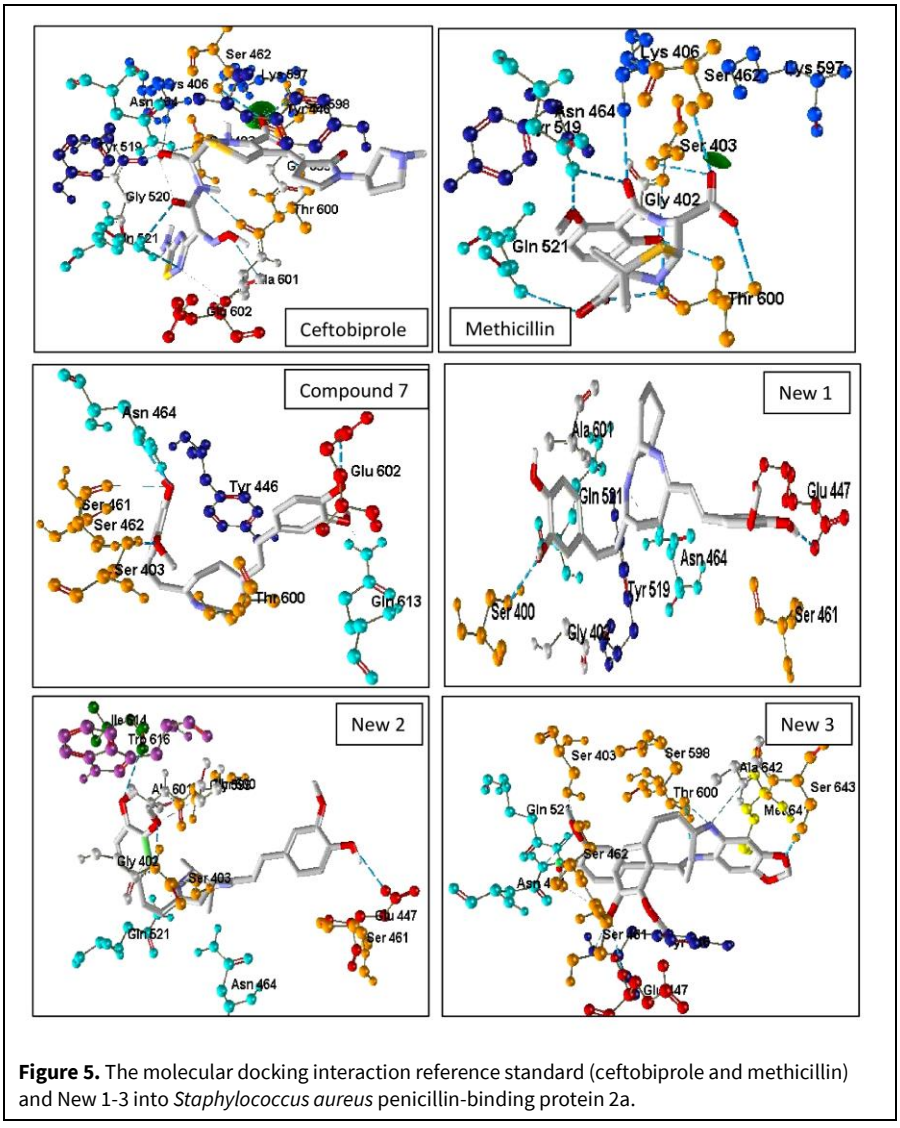


Figure 5. The molecular docking interaction reference standard (ceftobiprole and methicillin) and New 1-3 into *Staphylococcus aureus* penicillin-binding protein 2a.

formulations. Both indeed exhibit poor absorption in the GIT. In fact, of that, methicillin is not clinically used due to its high polarity, leading to significant nephrotoxic side effects.

New 1-3 compounds absorption prediction based on the Caco2 permeability value of New 1-3 compounds were better than ceftobiprole and methicillin. Caco2 cell lines are human epithelial colorectal adenocarcinoma cells that are cell monolayers often used as human intestinal mucosa models *in vitro* for permeability prediction for peroral drug absorption. Compounds are categorized as having high permeability if the Caco2 permeability value is $>8.10^{-6}$ cm/s (Pires et al., 2015). In addition to permeability parameters, water solubility parameters also play a crucial role in predicting absorption in the GIT. New 1-3 compounds have log S values ranging from -6.40 to -5.24, including in the moderately soluble category. In contrast, ceftobiprole has a log S value of -2.91, and methicillin has a log S value of -3.05, both classified as soluble. Based on the Biopharmaceutical Classification System (BCS), New 1-3 compounds could be included in BCS class II, with low permeability and high solubility characteristics. Therefore, the percentage of human intestinal absorption is classified as great or very good (>80%). Meanwhile, ceftobiprole and methicillin have a human intestinal absorption percentage of 24-45%, which was included in the poor-moderate absorption category. This is because both do not meet Lipinski's rule of five criteria and show lower permeability than New 1-3 compounds (Daina et al., 2017; Pires et al., 2015; Suhud et al., 2019).

The distribution prediction is based on the value of the blood-brain barrier (BBB) permeability of ceftobiprole and methicillin, and the New 1-3 compounds are estimated not to penetrate BBB. BBB is a protective monolayer of the brain, so chemical compounds cannot easily be entered into nerve cells. Drugs are divined to be categorized as readily cross BBB if the log BB value is >0.3. Ceftobiprole, methicillin, and New 1-3 compounds have a log BB value <0.3 (Pires et al., 2015). This is already expected because the compounds that can penetrate the BBB can certainly affect the central nervous system (CNS) and patient awareness. Several drugs are designed to penetrate the BBB, such as antibiotics for cases of meningitis infection, drugs for Parkinson's, and drugs for general anesthesia. These drugs are designed for MRSA infection so that it is not expected to penetrate the BBB (Trevor et al., 2015).

Cytochrome 450 (CYP) is an important detoxification enzyme found in the body and is widely found in the liver (Shargel et al., 2016; Trevor et al., 2015). The CYP enzymes activate and deactivate many drugs. Therefore, predicting the drug compounds, including whether or not they inhibit CYP, is very important. Some isoforms of the CYP are CYP 2D6 and 3A4. Both isoforms are drug metabolizers of almost >90%. This metabolism prediction is essential for screening whether the new compounds will most likely interact with other drugs in the metabolic phase. Ceftobiprole and methicillin are the standard drugs used for MRSA bacteria at *in vitro* assay. Both do not inhibit CYP 2D6 and CYP 3A4. Therefore, there are not many interactions with other drugs. Some drugs that are predicted to increase drug levels in the blood (bioavailability) due to the presence of CYP 3A4 inhibitors are antiarrhythmic drugs, antidepressants, azole antifungals, benzodiazepines, calcium channel blockers, cyclosporine, delavirdine, doxorubicin, efavirenz, erythromycin, estrogen, HIV protease inhibitors, nefazodone, paclitaxel, proton pump inhibitors, HMG-CoA reductase inhibitors, rifabutin, rifampicin, sildenafil, SSRIs, tamoxifen, trazodone, and vinca alkaloids (Trevor et al., 2015). Predicted metabolism of New 1-3 compounds did not inhibit the CYP 2D6 enzyme. However, New 1-3 compounds inhibited the CYP 3A4 enzyme.

New 1-3 compounds were predicted to be inhibitory for CYP 2C9 and CYP 2C19. Even though these two cytochromes metabolize drugs not as much as CYP 3A4, they still have to be careful because several drugs are predicted to increase drug levels in the blood (bioavailability) as a result of the presence of CYP 2C9 inhibitors, such as barbiturates, celecoxib, chloramphenicol, doxorubicin, ibuprofen, phenytoin, chlorpromazine, steroids, tolbutamide, and (S)-warfarin (Trevor et al., 2015). Meanwhile, several drugs are thought to increase drug levels in the blood (bioavailability) due to CYP2C9 inhibitors, for example, diazepam, phenytoin, topiramate, (R)-warfarin (Trevor et al., 2015).

The prediction of toxicity of New 1-3 compounds is that they are not hepatotoxic, while ceftobiprole and methicillin are hepatotoxic. The LD_{50} prediction also showed that New 1 was safer than others, with a value of LD_{50} = 2.709 mol/kg.

Overall, the results of pharmacokinetic prediction or ADMET prediction of New 1-3 compounds using pkCSM software and SIB online can be seen in Table 7.

From the QSAR and ADMET predictions, New 1 is predicted to have the most potential IC_{50} against MRSA bacteria and more safety than others because New 1 has the greatest LD_{50} for oral rat acute toxicity prediction and non-hepatotoxic. However, it is still

Table 7. The result of ADMET predictions.

Compound	Absorption			Distribution	Metabolism (CYP inhibitor)				Excretion	Toxicity	
	Caco2 Perm. 10^{-6} cm/s	Log S	HIA (%)	BBB Perm. (BB log)	2D6	3A4	2C9	2C19	Total clearance log mL/min/kg	Oral rat acute toxicity mol/kg (LD_{50})	Hepato toxicity
New 1	4.27	-5.65	89.71	-0.43	No	Yes	Yes	Yes	0.986	2.709	No
New 2	4.57	-5.24	89.98	-0.45	No	Yes	Yes	Yes	0.361	2.524	No
New 3	5.01	-6.40	100	-0.89	No	Yes	Yes	Yes	-0.081	2.559	No
Ceftobiprole	0.36	-2.91	24.09	-1.84	No	No	No	No	0.233	2.245	Yes
Methicillin	3.63	-3.05	45.34	-1.29	No	No	No	No	0.383	1.861	Yes

Perm: permeability; HIA: human intestinal absorption BBB: blood-brain barrier; CYP: cytochrome P450.

predicted to have more drug interaction than methicillin because New 1 was predicted as a CYP 3A4 inhibitor.

CONCLUSION

The best QSAR equation is pMIC = 0.812 (± 0.162) EHOMO + 5.443 (± 1.659), and the New 1 compound is the main candidate to be synthesized because it is very potential and has a better toxicity prediction than methicillin and ceftobiprole so that it can be tested on MRSA bacteria to prove the results of IC_{50} prediction.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Concepts or ideas	x	x	x		x	x		
Design		x		x	x	x		
Definition of intellectual content		x		x	x	x		
Literature search	x	x	x	x	x	x	x	x
Experimental studies			x	x				x
Data acquisition	x	x		x	x			
Data analysis		x	x	x	x			
Statistical analysis		x		x			x	
Manuscript preparation			x				x	
Manuscript editing	x	x	x				x	x
Manuscript review	x	x	x	x	x	x	x	x

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