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MOLECULAR DOCKING OF ANTIBACTERIAL ACTIVITY OF HEXAHYDRO-1,2,3-TRIAZINE DERIVATIVES

Candra Yulius Tahya[1,2], Wahyu Irawati[2], Karnelasatri[3]

[1]Medical Laboratory Technology (D4) Study Program, Faculty of Health Science, Universitas Pelita Harapan, Tangerang, Indonesia
[2]Biology Education Study Program, Faculty of Education, Universitas Pelita Harapan, Tangerang, Indonesia
[3]Pharmacy Diploma Study Program, Faculty of Health Sciences, Universitas Pelita Harapan, Tangerang, Indonesia

*Corresponding author: candra.tahya@uph.edu

Abstract

Hexahydro-1,3,5-triazine and its derivatives have attracted significant research interest due to their strong biological properties, including antibacterial, antimalarial, fungicidal, antiviral, anticancer, antimicrobial, antiamoebic, anti-inflammatory, and antitubercular activities. In this study, antibacterial activity was evaluated through molecular docking of sixteen novel hexahydro-1,3,5-triazine derivatives, alongside three control drug molecules obtained from the PDB database, targeting Penicillin-Binding Protein PBP2a (PDB ID: 1VQQ) from methicillin-resistant Staphylococcus aureus strain 27r. Docking simulations were performed using PyRx v1.1 with integrated AutoDock Vina. A targeted docking strategy was applied using a specific grid box centered on key amino acid residues identified from pharmacological control interactions. The drug potential of the test compounds was assessed using the Pa (Probability to be Active) value. Results from the Pa value analysis showed that several hexahydro-1,3,5-triazine derivatives exhibited higher average Pa values than the control drugs ceftaroline and ceftobiprole. Based on Lipinski's Rule of Five, six out of the sixteen compounds demonstrated favorable drug-likeness characteristics. According to the ADMET analysis, nearly all tested compounds exhibited acceptable pharmacokinetic profiles. Molecular docking results further revealed that thirteen of the sixteen synthesized compounds displayed strong binding affinity toward the target protein, with four compounds, specifically compounds 7, 16, 15, and 1, showing higher affinity than the control drug ceftobiprole. Overall, QSAR, ADMET, and molecular docking analyses suggest that several hexahydro-1,3,5-triazine derivatives, particularly compounds 7, 16, 15, and 1, possess promising potential as antibacterial agents.

Keywords: *Antibacterial, Molecular docking, Hexahydro-1,3,5-triazine.*

Introduction

Aryl amines are a group of chemical compounds containing at least one amino group attached to an alkyl hydrocarbon or aromatic system. Some aryl amines are produced through azo reduction by microorganisms found in the gut, skin, and environment (Chung, 2015). They also serve as structural components in several types of drugs. Certain aryl amine compounds act as precursors for the synthesis of hexahydro-

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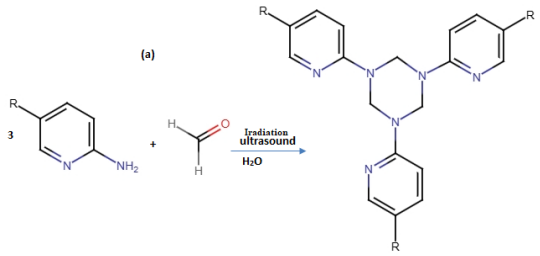
1,3,5-triazine derivatives, including several aminopyridine and aminopyrimidine compounds (Bae et al., 2021). The chemical classes aminopyridines and aminopyrimidines each contain a nitrogen atom attached to an amino group within a six-membered heterocyclic ring. Many natural substances, such as thiamine (vitamin B1) and several alkaloids, possess aminopyridine or aminopyrimidine core structures (Filho et al., 2021).

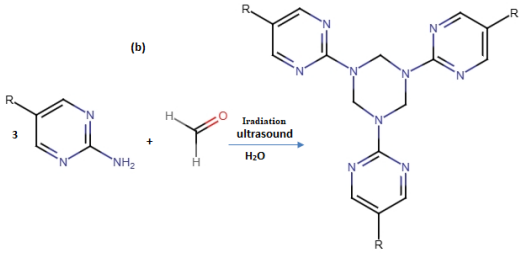
Hexahydro-1,3,5-triazine derivatives are compounds of considerable scientific interest because their triazine structural units are ubiquitous in natural and synthetic molecules (Pham et al., 2021). The triazine ring, composed of three nitrogen atoms at positions 1, 3, and 5, forms a six-membered structure that appears in numerous agrochemicals, including the herbicides prometon, simazine, atrazine, and cyanazine, as well as the insecticide menazone and the fungicide anilazine (Lim & Dolzhenko, 2014; Román et al., 2023). Due to their strong biological activities, including antibacterial, fungicidal, antimalarial, anticancer, antiviral, and antimicrobial properties, hexahydro-1,3,5-triazine derivatives have become a key focus of chemotherapeutic research (Pretty et al., 2004; Singh et al., 2012; Zhou et al., 2006). The synthesis of new hexahydro-1,3,5-triazine derivatives is expected to yield compounds with high antibacterial and antioxidant potential, as well as other biological and pharmacological activities. Developing novel derivatives increases the likelihood of discovering potent antibacterial agents, particularly in light of the growing global problem of antibiotic resistance.

In recent years, the excessive and improper use of antibiotics, combined with social and economic factors, has accelerated the spread of antibiotic-resistant bacteria (Mancuso et al., 2021). All tested compounds in this study were designed using available precursors sourced from Merck products. Sixteen compounds were selected as candidates for synthesis based on the reaction between aminopyridine or aminopyrimidine and formaldehyde (Ayrim et al., 2024), as shown in Eq. 1 and Eq. 2:

Eq. 1.



Eq. 2.



Bae et al. (2021) reported the synthesis of 13 hexahydro-1,3,5-triazinane derivatives, including 1,3,5-triphenyl-1,3,5-triazine; 3,5-tribenzyl-1,3,5-triazine; 1,3,5-tris(6-methylpyridin-2-yl)-1,3,5-triazine; 1,3,5-tri(quinolin-3-yl)-1,3,5-triazine; 1,3,5-tris(furan-2-ylmethyl)-1,3,5-triazine; and 1,3,5-tris(thiophen-2-ylmethyl)-1,3,5-triazine (Bae et al., 2021). These were synthesized through the cycloaddition of various amines with three molecules of formaldehyde, as illustrated in the above reactions (see **Eq. 1** and **Eq. 2**). Several other studies have also reported similar synthesis reactions to obtain novel triazine-based compounds (Ayrim et al., 2024; Salman et al., 2020). Building upon these findings, the present study aimed to evaluate 16 newly designed hexahydro-1,3,5-triazine derivatives as potential antibacterial agents through *in silico* molecular docking before selecting the most promising candidates for synthesis. Aryim et al. (2024) previously investigated the binding affinities of hexahydro-1,3,5-triazinane derivatives using the AutoDock 4.2 tool against glucosamine-6-phosphate synthase inhibitors to assess their antimicrobial activity and found that 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazinane exhibited the highest activity.

Therefore, this study conducted *in silico* antibacterial activity testing on 16 novel

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hexahydro-1,3,5-triazinane derivatives to identify the most promising candidate for future synthesis and *in vitro* antibacterial evaluation against various pathogenic bacterial species.

Methodology

Compounds Data Mining

The 2D structures of the bioactive compounds used in this study were drawn using Marvin Sketch. Furthermore, the Chemical Sketch Tool server (https://www.rcsb.org/chemical-sketch) was used to obtain the SMILES notation for each bioactive compound sample. The generation of 3D structures was performed using the Structure File Generator and SMILES Translator online server (https://cactus.nci.nih.gov/translate/). Meanwhile, the SMILES and 3D structures of the three drug controls, Penicillin G (CID: 5904), Ceftaroline (CID: 9852981), and Ceftobiprole (CID: 135413542), were collected from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/).

Prediction of Bioactive Compound Activity

The WAY2DRUG PASS prediction webserver (http://www.pharmaexpert.ru/passonline/predict.php) was used to evaluate the potential antibacterial activity of the compounds based on the Pa (Probability of Activity) value. The Pa value was considered during the data mining process, as it represents the likelihood of a compound exhibiting a particular biological activity.

ADMET Analysis

The pharmacokinetic characteristics of the sample compounds were analyzed, and each ligand's drug-likeness was assessed according to Lipinski's Rule of Five (Dong et al., 2018; Xiong et al., 2021). The evaluation was conducted using the ADMETLab 2.0 database (https://admetmesh.scbdd.com/service/evaluation/index).

Docking Analysis

The target protein used in this study was Penicillin-Binding Protein 2A (PBP2a) from methicillin-resistant *Staphylococcus aureus* strain 27r (PDB ID: 1VQQ), whose 3D structure was obtained from the Protein Data Bank (PDB) (https://www.rcsb.org/). A soluble derivative of PBP2a was selected as it possesses the highest-resolution structure for a high-molecular-mass PBP, with a resolution of 1.8 Å. This protein was chosen because it plays an essential role in antibiotic resistance in *S. aureus*, which was the target bacterium in this study. Protein preparation was conducted using Discovery Studio 2021 by removing ligands and water molecules, while ligand minimization was performed using PyRx v1.1. AutoDock Vina, integrated within PyRx v1.1, was employed for molecular docking. A specific grid box was designed for the targeted docking process based on the positions of key amino acid residues identified in the study by Kumar et al. (2014) (see **Table 1**). The grid box dimensions were adjusted according to the positions of amino acid residues in the target protein, guided by the control ligand from the PDB and further validated using PrankWeb (https://prankweb.cz/) (Jakubec et al., 2022). The binding affinity values represented the docking results. Additionally, the compound–protein interactions were visualized using BioVia Discovery Studio 2021.

Results and Discussion

Results and Discussion

Compounds Data Mining

This study utilized a total of 19 ligand compounds, consisting of 16 proposed synthetic compounds and 3 drug controls (see **Table 2**).

Bioactivity Analysis (QSAR)

The potential of a tested compound is represented by its Pa value. This value is determined by comparing the structure of the input compound with compounds that have been computationally proven to exhibit certain therapeutic activities. The bioactivity potential analysis was conducted using the Way2Drug PASS Server. A mean Pa value greater than 0.4 indicates that the compound is predicted to possess high

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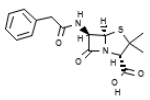
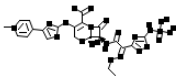
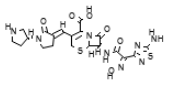
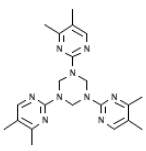
potential as an antibacterial agent, due to its strong structural similarity to compounds in the database that have been validated as antibacterial treatments (see **Figure 1**). The results of the Pa value analysis revealed that several synthetic compounds exhibited higher average Pa values than the control drugs Ceftaroline and Ceftobiprole. These synthetic compounds also demonstrated strong potential in mechanisms related to antibacterial activity, such as CYP2C19 induction, ubiquinol–cytochrome-c reductase inhibition, and sugar-phosphatase inhibition (Geronikaki et al., 2020; Watanabe et al., 2016).

Table 1. Grid Box Parameters for Molecular Docking

Protein	ID		X	Y	Z
PBP2a	1VQQ	Center	18.9137	30.9943	38.4751
		Dimensions	20	25	25
		Exhaustiveness	100	Mode	9

Table 2. Structural and SMILES Data of Ligands

No.	Compound	CID	SMILES
1	Penicillin G 	5904	CC1([C@@H](N2[C@H](S1)[C@@H](C2=O)NC(=O)CC3=CC=CC=C3)C(=O)O)C
2	Ceftaroline 	9852981	CCO/N=C(/C1=NSC(=N1)NP(=O)(O)O)\C(=O)N[C@H]2[C@@H]3N(C2=O)C(=C(CS3)SC4=NC(=CS4)C5=CC=[N+](C=C5)C)C(=O)[O-]
3	Ceftobiprole 	135413542	C1CNC[C@@H]1N2CC/C(=C\C3=C(N4[C@@H]([C@@H](C4=O)NC(=O)/C(=N\O)/C5=NSC(=N5)N)SC3)C(=O)O)/C2=O
4	Compound 1 	N/A	CC1=CN=C(N=C1C)N1CN(CN(C1)C1=NC=C(C)C(C)=N1)C1=NC(C)=C(C)C=N1
5	Compound 2	N/A	CC1=NC(=CC=C1CO)N1CN(CN(C1)C1=NC(C)=C(CO)C=C1)C1=CC=C(CO)C(C)=N1

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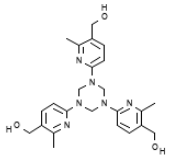
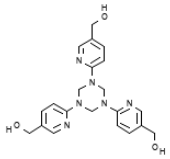
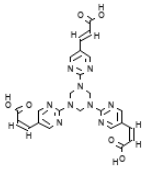
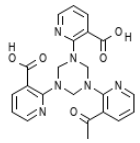
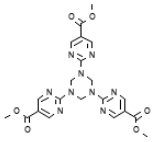
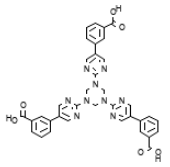
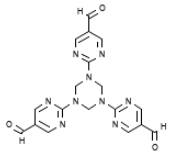
No.	Compound	CID	SMILES
			
6	Compound 3	N/A	OCC1=CC=C(N=C1)N1CN(CN(C1)C1=NC=C(CO)C=C1)C1=CC=C(CO)C=N1
			
7	Compound 4	N/A	OC(=O)\C=C\C1=CN=C(N=C1)N1CN(CN(C1)C1=NC=C(\C=C/C(O)=O)C=N1)C1=NC=C(\C=C/C(O)=O)C=N1
			
8	Compound 5	N/A	CC(=O)C1=C(N=CC=C1)N1CN(CN(C1)C1=C(C=CC=N1)C(O)=O)C1=C(C=CC=N1)C(O)=O
			
9	Compound 6	N/A	COC(=O)C1=CN=C(N=C1)N1CN(CN(C1)C1=NC=C(C=N1)C(=O)OC)C1=NC=C(C=N1)C(=O)OC
			
10	Compound 7	N/A	OC(=O)C1=CC(=CC=C1)C1=CN=C(N=C1)N1CN(CN(C1)C1=NC=C(C=N1)C1=CC(=CC=C1)C(O)=O)C1=NC=C(C=N1)C1=CC(=CC=C1)C(O)=O
			
11	Compound 8	N/A	[H]C(=O)C1=CN=C(N=C1)N1CN(CN(C1)C1=NC=C(C=N1)C([H])=O)C1=NC=C(C=N1)C([H])=O
			
12	Compound 9	N/A	OB(O)C1=CN=C(N=C1)N1CN(CN(C1)C1=NC=C(C=N1)B(O)O)C1=NC=C(C=N1)B(O)O

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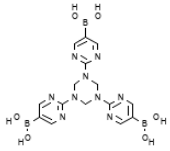
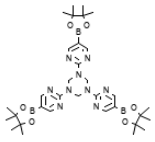
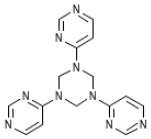
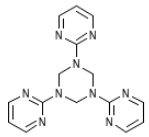
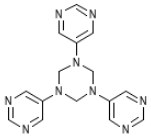
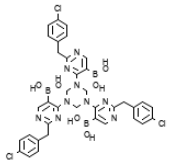
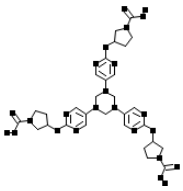
No.	Compound	CID	SMILES
			
13	Compound 10	N/A	CC1(C)OB(OC1(C)C)C1=CN=C(N=C1)N1CN(CN(C1)C1=NC=C(C=N1)B1OC(C)(C)C(C)(C)O1)C1=NC=C(C=N1)B1OC(C)(C)C(C)(C)O1
			
14	Compound 11	N/A	C1N(CN(CN1C1=NC=NC=C1)C1=NC=NC=C1)C1=CC=NC=N1
			
15	Compound 12	N/A	C1N(CN(CN1C1=NC=CC=N1)C1=NC=CC=N1)C1=NC=CC=N1
			
16	Compound 13	N/A	C1N(CN(CN1C1=CN=CN=C1)C1=CN=CN=C1)C1=CN=CN=C1
			
17	Compound 14	N/A	OB(O)C1=CN=C(CC2=CC=C(Cl)C=C2)N=C1N1CN(CN(C1)C1=NC(CC2=CC=C(Cl)C=C2)=NC=C1B(O)O)C1=NC(CC2=CC=C(Cl)C=C2)=NC=C1B(O)O
			
18	Compound 15	N/A	OC(=O)N1CCC(C1)OC1=NC=C(C=N1)N1CN(CN(C1)C1=CN=C(OC2CCN(C2)C(O)=O)N=C1)C1=CN=C(OC2CCN(C2)C(O)=O)N=C1
			
19	Compound 16	N/A	OC1=C(C=C(Br)C=C1)C1=CC=NC(=N1)N1CN(CN(C1)C1=NC=CC(=N1)C1=C(O)C=CC(Br)=C1)C1=NC=CC(=N1)C1=C(O)C=CC(Br)=C1

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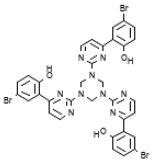
No.	Compound	CID	SMILES
			

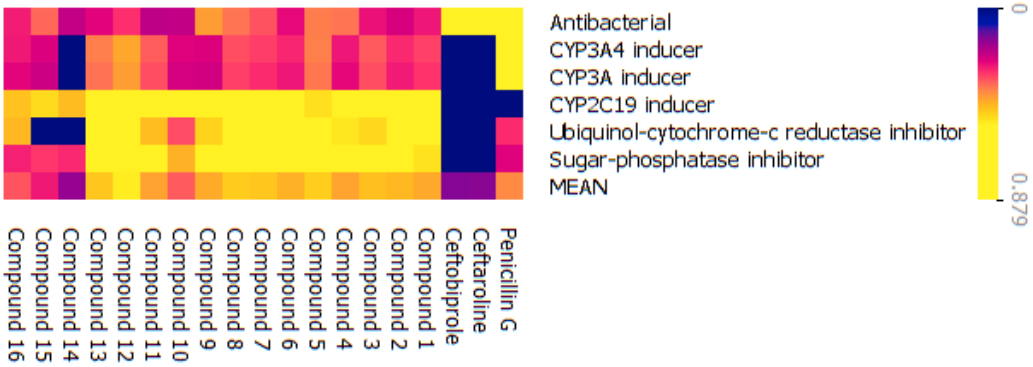


Figure 1. Results of bioactivity analysis showing the potential of the compounds as antibacterial agents.

ADMET Analysis

Based on Lipinski's Rule of Five, the analysis results indicated that six out of the sixteen tested compounds exhibited good drug-likeness characteristics. However, according to Pfizer's standards, all compounds in this study demonstrated these properties (see **Table 4**). Drug-like and non–drug-like compounds can be distinguished using Lipinski's Rule of Five, which predicts whether a compound is likely to be successfully metabolized based on its molecular characteristics (Lipinski et al., 2001). Compounds that meet at least two of the five main criteria are considered to comply with this rule. These criteria include: 1) A molecular weight of less than 500 Daltons; 2) High lipophilicity (LogP less than 5); 3) No more than 5 hydrogen bond donors; and 4) No more than 10 hydrogen bond acceptors. Meanwhile, the ADMET analysis (Absorption, Distribution, Metabolism, Excretion, and Toxicity) showed that most of the compounds possessed favorable pharmacokinetic properties. However, several compounds demonstrated potential toxicity to the liver, including drug-induced liver injury (DILI) and hepatotoxicity (H-HT), as well as potential carcinogenic effects. It is important to note that poor drug-likeness or suboptimal ADMET properties do not necessarily imply that a compound lacks pharmacological potential. Instead, such results may indicate slightly reduced bioavailability, often due to the need for passive absorption. Nonetheless, this limitation can be overcome by applying optimized drug-delivery systems to enhance bioavailability.

Docking Analysis

The molecular docking analysis revealed that, in general, 13 out of 16 synthetic compounds exhibited strong affinity toward the target protein PBP2a (see **Table 3**). This prediction was based on the binding energy of these compounds being less than or equal to the threshold value of –7 kcal/mol (Trott & Olson, 2010). Binding energies below this threshold indicate that the ligand–protein interactions are more stable and are likely to form efficiently and rapidly. Furthermore, when compared with the three drug controls, four of the synthetic compounds demonstrated better affinity than Ceftobiprole (Kumar et al., 2014), while three other compounds showed better affinity than Ceftaroline (Otero et al., 2013).

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Table 3. Binding Affinity between Target Protein (PBP2a) and Control/Synthetic Ligands

No.	Ligand	Binding Affinity (kcal/mol)
1	Compound 7	-11
2	Compound 16	-11
3	Compound 15	-10.2
4	Compound 1	-8.5
5	**Ceftobiprole**	-8.3
6	Compound 2	-8.1
7	Compound 4	-8.1
8	Compound 5	-7.9
9	**Ceftaroline**	-7.9
10	Compound 3	-7.8
11	Compound 6	-7.7
12	Compound 8	-7.6
13	**Penicillin G**	-7.6
14	Compound 11	-7.1
15	Compound 13	-7.1
16	Compound 12	-7
17	Compound 9	N/A
18	Compound 10	N/A
19	Compound 14	N/A

Note: N/A (not applicable) indicates that compounds 9, 10, and 14 contained boron (B) atoms, which rendered them incompatible with AutoDock during docking simulations.

Table 4. Results of Drug-Likeness and ADMET Analysis of Potential Compounds Using AdmetLab 2.0

No.	Compound	Drug-Likeness		Absorption		Distribution		Metabolism				Excretion	Toxicity			
		Lipinski	Pfizer	HIA	Caco-2	BBB	PPB	CYP1A2-inh	CYP2C19-inh	CYP2C9-inh	CYP3A4-inh	CL	H-HT	DILI	FDAMDD	Carcinogenicity
1	**Penicillin G**	**ACC**	**ACC**	**0.02**	**-5.798**	**0.045**	**68.09 %**	**0.009**	**0.03**	**0.029**	**0.013**	**6.206**	**0.143**	**0.96**	**0.002**	**0.011**
2	**Ceftaroline**	**REJ**	**ACC**	**0.997**	**-6.037**	**0.347**	**61.91 %**	**0.087**	**0.119**	**0.121**	**0.016**	**1.692**	**0.957**	**0.994**	**0.333**	**0.244**
3	**Ceftobiprole**	**REJ**	**ACC**	**0.946**	**-6.324**	**0.205**	**22.43 %**	**0.017**	**0.166**	**0.127**	**0.021**	**1.373**	**0.994**	**0.996**	**0.812**	**0.834**
4	Compound 1	ACC	ACC	0.015	-4.662	0.005	98.45 %	0.567	0.423	0.201	0.316	4.611	0.938	0.994	0.818	0.389

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5	Compound 2	ACC	ACC	0.011	-5.145	0.28	79.51 %	0.46	0.051	0.002	0.137	4.131	0.984	0.991	0.872	0.7
6	Compound 3	ACC	ACC	0.105	-4.988	0.248	47.72 %	0.365	0.302	0.053	0.052	3.135	0.988	0.994	0.564	0.437
7	Compound 4	REJ	ACC	0.022	-5.924	0.016	91.21 %	0.373	0.016	0.026	0.032	1.455	0.968	0.999	0.244	0.844
8	Compound 5	ACC	ACC	0.137	-6.096	0.042	55.18 %	0.157	0.189	0.613	0.07	1.442	0.956	0.999	0.009	0.053
9	Compound 6	ACC	ACC	0.007	-4.554	0.88	92.89 %	0.416	0.878	0.206	0.543	5.222	0.362	0.998	0.915	0.295
10	Compound 7	REJ	ACC	0.006	-5.852	0.002	99.50 %	0.392	0.025	0.029	0.004	0.328	0.856	1	0.92	0.153
11	Compound 8	ACC	ACC	0.01	-5.288	0.903	85.52 %	0.752	0.06	0.029	0.084	2.621	0.221	0.995	0.866	0.865
12	Compound 9	REJ	ACC	0.984	-5.669	0.273	98.10 %	0.454	0.039	0.036	0.011	1.029	1	0.999	0.962	0.998
13	Compound 10	REJ	ACC	0.032	-4.779	0.728	81.03 %	0.043	0.072	0.092	0.059	5.636	1	1	0.922	1
14	Compound 11	ACC	ACC	0.059	-4.955	0.942	32.66 %	0.625	0.768	0.021	0.673	3.675	0.983	0.998	0.603	0.084
15	Compound 12	ACC	ACC	0.014	-4.291	0.501	76.43 %	0.41	0.173	0.586	0.008	2.728	0.728	0.996	0.836	0.816
16	Compound 13	ACC	ACC	0.024	-5.62	0.613	35.02 %	0.441	0.674	0.027	0.936	3.145	0.996	0.999	0.113	0.02
17	Compound 14	REJ	ACC	0.763	-5.835	0.005	101.17 %	0.559	0.319	0.297	0.107	2.652	1	1	0.955	0.968
18	Compound 15	REJ	ACC	0.02	-6.238	0.026	71.09 %	0.003	0.033	0.002	0.009	0.866	1	1	0.981	0.722
19	Compound 16	REJ	ACC	0.056	-4.978	0.001	104.04 %	0.658	0.894	0.303	0.196	1.303	0.75	0.997	0.953	0.148

Description:
ACC (Accepted): The compound exhibited good drug-likeness characteristics.
REJ (Rejected): The compound displayed poor bioavailability and might possess toxic potential when acting as a single compound.

Table 5 presents the interactions formed between the target protein (PBP2a) and each of the top four ligand candidates, along with the control drug Ceftobiprole. Based on the types of bonds observed, in addition to hydrogen bonds, hydrophobic and van der Waals interactions were the most dominant. Residues shown in bold represent key amino acid residues from the Ceftobiprole drug control (Kumar et al., 2014), as well as residues predicted by PrankWeb that were preserved by the synthetic ligands through the same bonding type. Residues shown in bold italics represent key amino acids from Ceftobiprole and PrankWeb predictions that were retained by the sample but exhibited variations in bond type or distance. Analysis of the active-site amino acid residues indicated that high binding affinity and low binding energy were supported by the compounds' ability to maintain interactions with these key residues, thereby mimicking the activity of the control drug. Mapping of the key residues also revealed that HIS293 and VAL277 were the most critical amino acids for effective inhibition of the PBP2a protein (**in Table 5**). **Figures 2–6** illustrate the 3D visualization results of the protein–ligand complexes between PBP2a and the selected sample or control ligands.

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Table 5. Interactions of Amino Acid Residues Generated in the Target Protein with Control Ligand and Top Five Compounds

Ligand	Interaction				
	van der Waals	**Hydrogen Bond**	**Hydrophobic**	**Electrostatic**	**Unfavorable**
PrankWeb	A_148 A_149 A_150 A_151 A_165 A_239 A_240 A_241 A_256 A_277 A_293				
Ceftobiprole (Kumar dkk., 2014)		ASP275 GLN292 HIS293	ASN146 GLU294 ASP295 TYR297 LYS273 VAL277		
Compound 7	*A:GLU150* *A:ARG151* *A:SER149* *A:THR165* *A:GLU294* A:TYR105 A:ILE144 *A:GLU239*	*A:ASP295* A:GLN292	A:TYR297 A:TYR272 ***A:HIS293*** **A:VAL277** *A:LYS148* A:LYS273 A:ALA276	***A:HIS293***	*A:ASN146*
Compound 16	*A:GLN292* *A:LYS148* *A:GLU294* A:LYS319	*A:SER149* *A:LYS273* *A:ASN146*	A:TYR272 A:TYR297 ***A:HIS293*** A:LYS289 **A:VAL277** A:LYS273 A:ALA276 A:TYR105	***A:HIS293*** *A:ASP295*	A:GLY296
Compound 15	A:ILE144 A:GLU145 *A:ASN146* *A:ASP275* *A:ARG241* *A:VAL256* A:LYS289 *A:GLU150* ***A:HIS293*** *A:GLN292* *A:GLU294* A:GLY296	A:TYR105 *A:ARG151*	A:LYS273 A:ALA276 **A:VAL277** A:TYR272 A:TYR297	*A:ASP295*	
Compound 1	*A:ASP295* *A:SER149*	*A:GLU294*	A:VAL277 *A:LYS148* **A:VAL277** A:ALA276 A:LYS273 A:TYR272 ***A:HIS293***	A:HIS293 *A:ASP275*	
Ceftobiprole	A:ILE144 *A:TYR297* A:GLY296 *A:GLU294* A:ALA276 ***A:VAL277*** *A:ARG151* *A:GLU150* *A:THR165*	A:TYR105 *A:GLU239* *A:SER149* **A:HIS293** *A:ASP295*	*A:LYS148* ***A:HIS293***		*A:ASN146*

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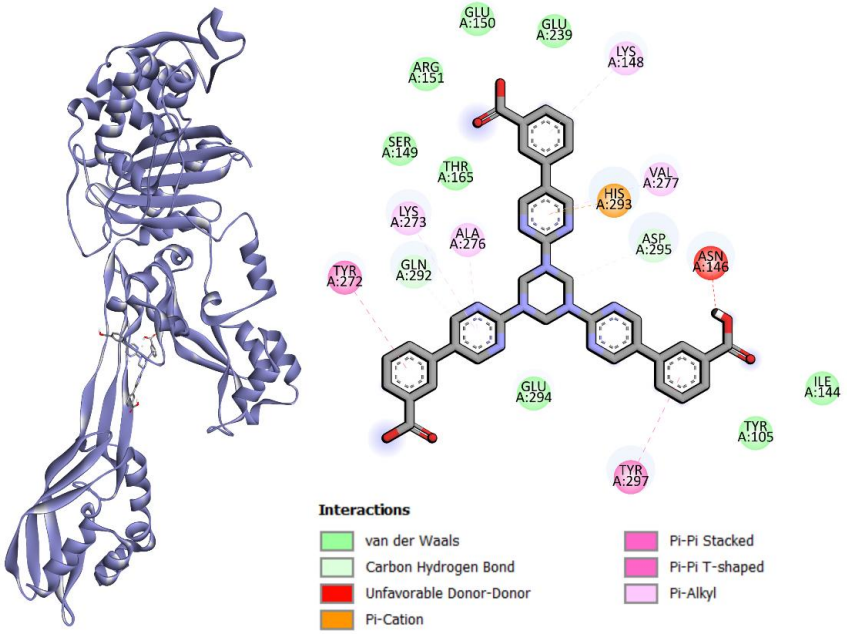
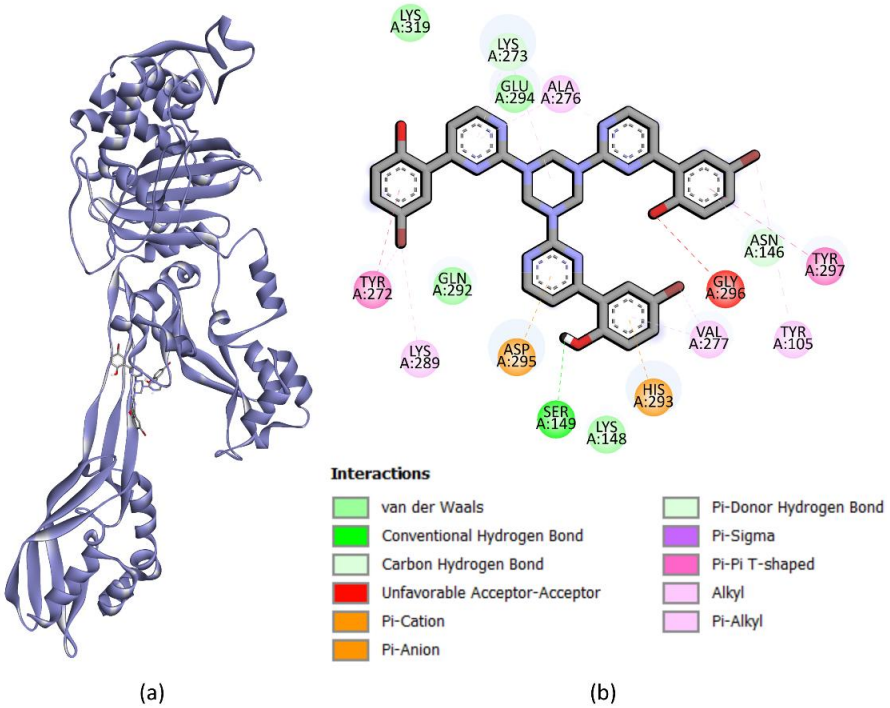


(a) (b)

Figure 2. Visualization of docking results between PBP2a protein and Compound 7: (a) 3D visualization; (b) types of bonds formed between ligand and protein.



(a) (b)

Figure 3. Visualization of docking results between PBP2a protein and Compound 16: (a) 3D visualization; (b) types of bonds formed between ligand and protein.

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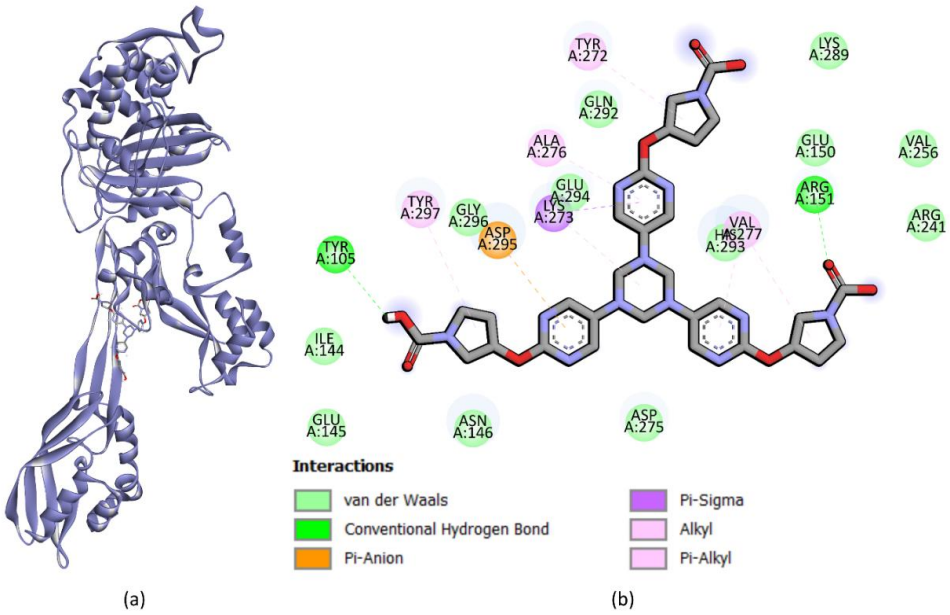

Figure 4. Visualization of docking results between PBP2a protein and Compound 15: (a) 3D visualization; (b) types of bonds formed between ligand and protein..

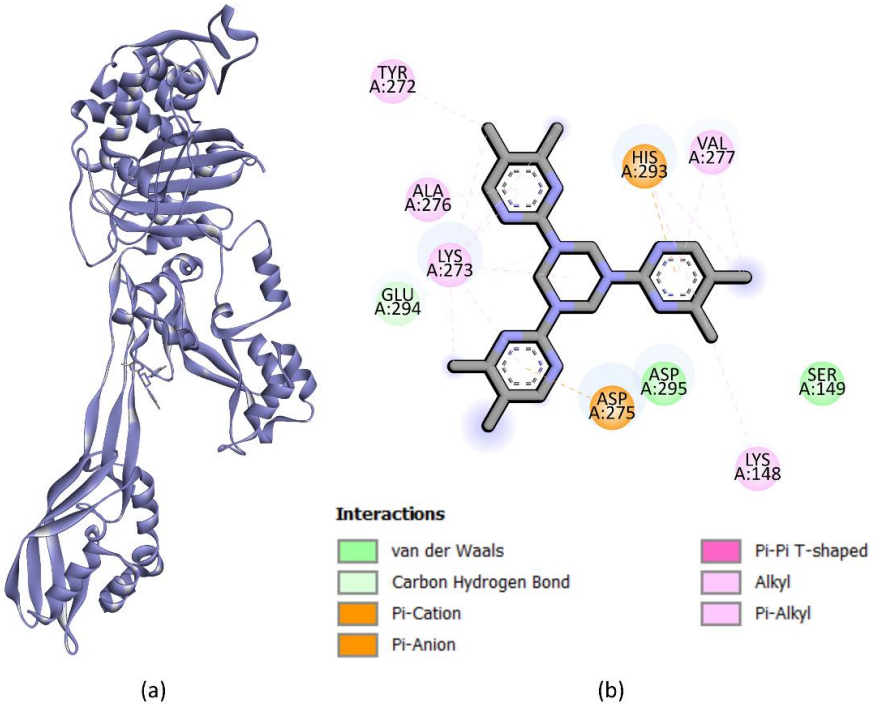

Figure 5. Visualization of docking results between PBP2a protein and Compound 15: (a) 3D visualization; (b) types of bonds formed between ligand and protein.

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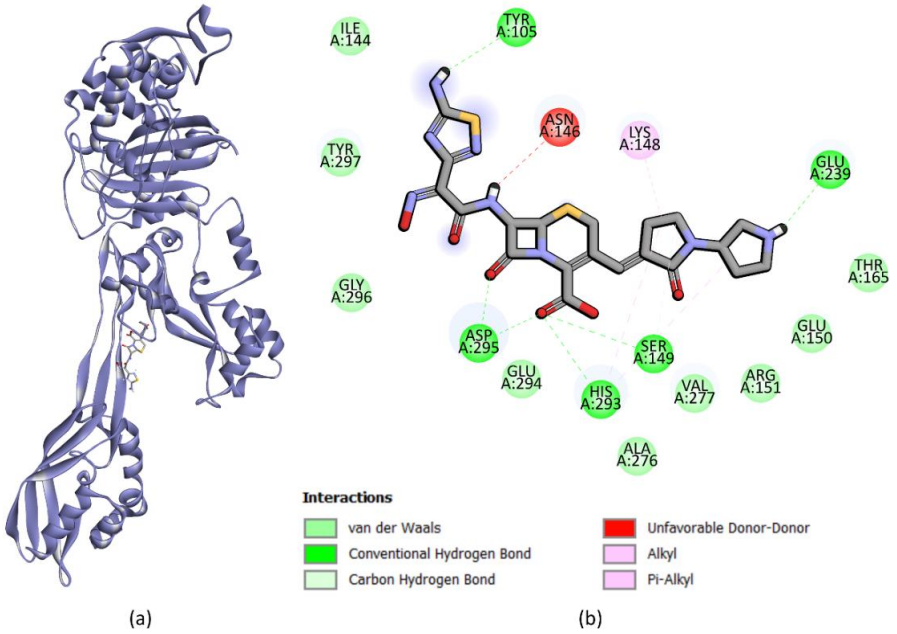

Figure 6. Visualization of docking results between PBP2a protein and control ligand Ceftobiprole: (a) 3D visualization; (b) types of bonds formed between ligand and protein.

Conclusion

The results of QSAR, ADMET, and molecular docking analyses showed that the synthetic compounds, particularly compounds 7, 16, 15, and 1, exhibit potential antibacterial activity. The binding affinities of compounds 7, 16, 15, and 1 were recorded at −11, −11, −10.2, and −8.5 kcal/mol, respectively, which were stronger than those of the control drugs penicillin G, ceftaroline, and ceftobiprole. These four compounds were found to interact with the same key residues, HIS293 and VAL277, which are critical amino acids that must be bound by PBP2a inhibitor compounds. Overall, the thirteen synthesized compounds demonstrated potential antibacterial mechanisms as CYP2C19 regulators, ubiquinol–cytochrome c reductase inhibitors, sugar-phosphatase inhibitors, and PBP2a inhibitors.

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